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Medical technologies guidance

MT476 UroShield for preventing catheter-associated urinary tract infections

External Assessment Centre report

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Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AE	Adverse event
BPH	Benign prostatic hyperplasia
CABSI	Catheter-associated blood stream infection
CAUTI	Catheter-associated urinary tract infection
CI	Confidence interval
CFU	Colony-forming unit
EAC	External Assessment Centre
ED	Emergency Department
FDA	Food and Drug Administration
FG	French gauge
HCAI	Healthcare-associated infection
ISC	Intermittent self-catheterisation
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MDR	Multi-drug resistant/resistance
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PI	Principal Investigator
PICO	Population, Intervention, Comparator, Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RR	Risk ratio
SAE	Serious adverse event
SCI	Spinal cord injury
SD	Standard deviation
TGA	Therapeutic Goods Association
UTI	Urinary tract infection
VAS	Visual analogue scale

Vs	Versus

Executive summary

The UroShield device is a disposable ultrasound device comprising 2 parts (a driver and a single use actuator) that can be used with indwelling catheters of any material. It is designed to reduce the risk of catheter-associated urinary tract infection (CAUTI) when it is attached to the external portion of the catheter. It does this by generating and propagating low-frequency, low-intensity ultrasonic surface acoustic waves throughout the catheter, reducing bacterial colonization and biofilm formation by interfering with the attachment of bacteria. UroShield is intended for prophylactic use only and should not be used to treat active infections. It would be an addition to current standard care for indwelling catheters. Adoption of the technology would not require a significant change in current NHS care pathways, it is relatively simple to operate and little time would be required for training and implementation.

Indwelling catheters are required for a variety of reasons, and may be used in a community or hospital setting. People with indwelling catheters may have long-term catheters (defined as >28 days) or short-term catheters (defined as ≤28 days) (NICE 2017; Loveday et al. 2014).

The clinical experts have indicated that the main benefit from UroShield is most likely to be seen in a community setting, where people are more likely to have long-term catheters and be more experienced with self-management, and in people at high risk of CAUTI (including those who have previously experienced recurrent infections). The estimated prevalence of long-term catheter users in the community setting in the UK is over 90,000, and prevalence increases with increased age, especially amongst men (Gage et al. 2016). Clinical experts indicate there is no standard definition for 'high risk' and that identifying any specific risk factors was difficult. However, the company proposed a number of parameters that might contribute to this consideration, including factors such as gender, previous history of urinary tract problems, neurological conditions, previous UTIs, previous and/or current abnormal voiding patterns, current catheter history, incontinence and/or co-morbid conditions such as diabetes or immunosuppression.

The clinical evidence is currently very limited both in quality and quantity, although all studies are relevant to the decision problem and meet the PICO elements of the

scope. There is limited evidence from 3 studies that UroShield can reduce in bacteriuria and infections in people with long-term catheters (Markowitz et al. 2018; da Silva et al. 2021; Nagy et al. 2011). The evidence for the benefit of UroShield in patients with short-term catheters is very limited and does not suggest any clinical benefit. No other subgroup analysis or risk group analysis is available.

Patient reported outcomes in one study suggest that people find the device easy to use although there were some comments around battery life and not knowing how much battery life was remaining, as well as the device being uncomfortable to use at night. Feedback broadly indicated that people experienced reduced risk and frequency of CAUTIs and an extension of time between catheter changes. There also appears to be a positive impact on quality of life, with patients reporting they became more social and independent and less concerned about their condition.

The company evaluated the potential for cost savings in 6 combinations of population and setting; 4 in hospital and 2 in the community. The cost of implementing the technology comprised the cost of the driver and actuator, balanced against the treatment costs of CAUTIs avoided by the use of UroShield.
The effectiveness of UroShield at preventing CAUTIs needing treatment was based on the meta-analysis of 4 studies that used asymptomatic bacteriuria as a proxy outcome measure. Other significant uncertainties were the base rates of CAUTI infection and the cost of hospital treatment. Despite these uncertainties, scenarios with high treatments costs or high infection rates (eg ICU, long-term catheter durations in hospital settings or community patients with recurrent infections) were cost-saving and relatively robust to changes made in the sensitivity analysis. UroShield was robustly cost-incurring in the general community setting due to low treatment costs. For the general hospital population and in short-term catheter duration in hospital, cost-savings were marginal and therefore uncertain

Overall, the EAC consider that the UroShield device is safe and easy for patients to use, and shows promise for the prevention of CAUTIs. There is currently not enough good quality evidence to support routine adoption of the UroShield device. However, the EAC consider further research within an NHS setting would be beneficial.

1 Decision problem

The company and the EAC have not proposed any variation to the decision problem specified in the scope. Details of the decision problem as outlined in the scope, including details of the population, intervention, comparator and outcomes under investigation can be found in Appendix A.

2 Overview of the technology

The UroShield device is a disposable ultrasound device that can be used with catheters made of any material and sizes 12-22 French Gauge (FG). The device comprises 2 components:

- A driver (battery or AC powered portable unit) which provides power. The driver is not patient specific and can be re-used by multiple patients.

- Single use actuator (clipped to the external portion of indwelling catheter) which generates the ultrasonic waves. The actuator is patient-specific but can be used for up to 30 days. If the catheter is replaced within a 30-day period the actuator can be removed and reattached to the new catheter.

UroShield is designed to reduce the risk of catheter associated urinary tract infection (CAUTI) by reducing bacterial colonization and biofilm formation on indwelling urinary catheters. A biofilm forms when planktonic bacteria adhere to the surface of an indwelling catheter and can begin within hours of catheter placement. Established biofilms are highly resistant to antibiotics and to the body's own immune system. Any patient with an indwelling urinary catheter is at risk of biofilm formation and the longer the catheter remains in place the greater the tendency for biofilm formation and associated urinary tract infection. The UroShield device attaches to the external portion of any indwelling catheter and generates and propagates low frequency, low intensity ultrasonic surface waves throughout the catheter. This interferes with the attachment of bacteria which in turn prevents infection developing,

reduces catheter encrustation and blockages and decreases or eliminates the need for antibiotics. The company claim that this in turn reduces the costs associated with indwelling catheter complications that may lead to increased medication and extended hospital stays.

UroShield has current CE mark authorization as a class IIa medical device, which is valid until May 2024. The company has confirmed that there are plans to apply for and achieve the UKCA mark in advance of the mandatory date so that they are fully compliant with UK regulations post 2023.

Since its original launch in 2015, there have been some refinements to device functionality (table 1). The company has confirmed that none of these changes would be expected to affect the mechanism of action or impact on clinical outcomes. Additional information provided by the company indicated that there are no changes in energy type or mode of operation. The product labelling and Risk Analysis have been updated to reflect the changes. In addition, UroShield 3.0 was subjected to electrical safety testing and found to be in conformity with IEC 60601-1-11:2015, IEC 60601-1-6:2010, IEC 60601-1-6:2010/AMD1:2013, IEC 606011:2005, IEC 60601-1:2005/AMD1:2012. The EAC consider that, based on the information provided, none of the changes affect the mechanism of action of the device. The company also indicated that all of the NHS patients presently using UroShield are already using the upgraded UroShield 3.0 or are in the process of being upgraded to the UroShield 3.0 device.

Table 1: Versions and changes to the UroShield device

Version(s)	Launched	Features
39.05	7 November 2019	1. Firmware improvement self-regulation, hardware product upgrade following commercial feedback 2. Implementation of EMC IEC 60601-1-2 rev. 4.0 standard
37.05	30 April 2019	Improvement UroShield Driver Functionality
35.05	5 February 2018	Changing screen saver in the Working Mode

Version(s)	Launched	Features
33.05	7 December 2015	Improvement of self-regulation function, repair software bugs during USB connection
32.05	6 May 2015	Additional function to working mode – battery charging during driver operation. Functionality upgrade to firmware rev.32.05 from base driver FD – 14A firmware rev.31

3 Clinical context

Indwelling catheters are required for a variety of reasons and people with indwelling catheters may have long-term catheters, defined as >28 days, or short-term catheters, defined as ≤28 days (NICE 2017, Loveday et al. 2014). People with indwelling catheters are at risk of catheter-associated urinary tract infection (CAUTI), with the EPIC3 guidelines reporting a 5% increase in risk for every day the catheter is in place in an acute care setting (Loveday et al. 2014). Gage et al. (2016) reported an estimated prevalence of long-term catheter users in the community setting in the UK of over 90,000, and prevalence increases with increased age, especially amongst men. This is extrapolated from a total of 583 long term catheter users (329 south England, 254 west England) identified from 404,328 people registered with GP practices. Reasons for long term catheterization was primarily neurological (62.9%), with women more likely to have a catheter for neurological reasons than men (71.8% vs.56.2%). Most were urethral catheters (59.7%), however women were more likely to have a suprapubic catheter compared with men (56.4% vs. 29.3%), and this is supported by the clinical experts (see correspondence log).

Getliffe and Newton (2006) carried out a mapping exercise to identify local, national, and international sources of data on CAUTI. They also conducted a retrospective prevalence survey of CAUTIs in community settings, across three Primary Care Trusts in England during October 2004, and reported an overall prevalence rate of 8.5%. Smith et al. (2019) reports estimated 5005 (95% CI 4509-5695) patients admitted to hospital with community-onset

catheter-associated blood stream infection (CABSI), with a total estimated 7529 (95% CI 6857-8622) cases of CABSI across all trusts.

In the UK hospital setting, from the EPIC3 guidelines (Loveday et al 2014), an estimated 15-25% of patients have a urinary catheter during their hospital stay. Bacteriuria develops in approximately 30% of patients, and 24% (95% CI 23–29%) of these will develop symptoms of CAUTI. Smith et al (2019) report estimated there were approximately 997,814 (UI 977,306-1,018,205) catheterized patients and that approximately 3.8% (95% CI 3.0-4.7%) of inpatients with catheters in the UK developed hospital-onset CAUTI, accounting for 38,084 (95% CI 30,236-46,541) of a total 52,085 (95% CI 42,967-61,360) CAUTIs across all Trusts. The same study reported that catheterized patients with longer length of stay (LOS) were more likely to develop CAUTI, ranging from 3.1% (95% CI 2.4-3.9%) in patients with LOS of two days to 13.2% (95% CI 8.0-21.2%) for patients with LOS lasting ≥40 days. An estimated 4.8% (95% CI 4.1-6.3%) of inpatients with CAUTI further developed hospital-onset CABSI, representing 2524 infections (95% CI 2319-2956).

The EAC identified NICE Guidance and SIGN Guidance which are relevant to the decision problem. Additional guidance is available from the European Association of Urology (Bonkat et al. 2021) and EPIC3 (Loveday et al. 2014).

- NICE Clinical Guideline 139 [CG139]: Healthcare-associated infections: prevention and control in primary and community care (NICE 2017)
- NICE Guideline 113 [NG113]: Urinary tract infection (catheter-associated): antimicrobial prescribing (NICE 2018a)
- SIGN Guideline 88 [SIGN88]: Management of suspected bacterial urinary tract infection in adults (Healthcare Improvement Scotland 2006)

- EPIC3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England (Loveday et al. 2014)
- European Association of Urology (EAU) Guidelines: Urology Infections (Bonkat et al. 2021)

Specific recommendations relevant to the decision problem are detailed in table 2.

Table 2: Recommendations from Current Guidance

Guideline	Potentially Relevant Recommendations
NICE CG139 (NICE 2017)	1.2.5.1: Indwelling catheters should be connected to a sterile closed urinary drainage system or catheter valve. [2003] 1.2.5.2: Healthcare workers should ensure that the connection between the catheter and the urinary drainage system is not broken except for good clinical reasons (for example changing the bag in line with the manufacturer's recommendations). [2003] 1.2.5.3: Healthcare workers must decontaminate their hands and wear a new pair of clean, non-sterile gloves before manipulating a patient's catheter, and must decontaminate their hands after removing gloves. [2003] 1.2.5.4: Patients managing their own catheters, and their carers, must be educated about the need for hand decontamination before and after manipulation of the catheter, in accordance with the recommendations in the standard principles section (section 1.1). [2003, amended 2012] 1.2.5.5: Urine samples must be obtained from a sampling port using an aseptic technique. [2003] 1.2.5.6: Urinary drainage bags should be positioned below the level of the bladder, and should not be in contact with the floor. [2003] 1.2.5.7: A link system should be used to facilitate overnight drainage, to keep the original system intact. [2003] 1.2.5.8: The urinary drainage bag should be emptied frequently enough to maintain urine flow and prevent reflux, and should be changed when clinically indicated. [2003] 1.2.5.9: The meatus should be washed daily with soap and water. [2003] 1.2.5.10: To minimise the risk of blockages, encrustations and catheter-associated infections for patients with a long-term indwelling urinary catheter:

Guideline	Potentially Relevant Recommendations
	• develop a patient-specific care regimen • consider approaches such as reviewing the frequency of planned catheter changes and increasing fluid intake • document catheter blockages. [new 2012] 1.2.5.11: Bladder instillations or washouts must not be used to prevent catheter-associated infections. [2003] 1.2.5.12: Catheters should be changed only when clinically necessary or according to the manufacturer's current recommendations. [2003] 1.2.5.13: When changing catheters in patients with a long-term indwelling urinary catheter: • do not offer antibiotic prophylaxis routinely • consider antibiotic prophylaxis[17] for patients who: o have a history of symptomatic urinary tract infection after catheter change or o experience trauma[18] during catheterization. [new 2012]
NICE NG113 (NICE 2018a)	**Managing catheter-associated urinary tract infection** 1.1.1: Be aware that: • a catheter-associated urinary tract infection (UTI) is a symptomatic infection of the bladder or kidneys in a person with a urinary catheter • the longer a catheter is in place, the more likely bacteria will be found in the urine; after 1 month nearly all people have bacteriuria • antibiotic treatment is not routinely needed for asymptomatic bacteriuria in people with a catheter[1]. 1.1.2: Give advice about managing symptoms with self-care (see the recommendations on self-care) to all people with catheter-associated UTI. **Treatment** 1.1.3: Consider removing or, if this cannot be done, changing the catheter as soon as possible in people with a catheter-associated UTI if it has been in place for more than 7 days. Do not allow catheter removal or change to delay antibiotic treatment. 1.1.4: Obtain a urine sample before antibiotics are taken. Take the sample from the catheter, via a sampling port if provided, and use an aseptic technique (in line with the NICE guideline on healthcare-associated infections). • If the catheter has been changed, obtain the sample from the new catheter. • If the catheter has been removed, obtain a midstream specimen of urine.

Guideline	Potentially Relevant Recommendations
	1.1.5: Send the urine sample for culture and susceptibility testing, noting a suspected catheter-associated infection and any antibiotic prescribed. 1.1.6: Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract, or immunosuppression • previous urine culture and susceptibility results • previous antibiotic use, which may have led to resistant bacteria. 1.1.7: When urine culture and susceptibility results are available: • review the choice of antibiotic and • change the antibiotic according to susceptibility results if the bacteria are resistant, using narrow-spectrum antibiotics wherever possible. **Reassessment** 1.1.9: Reassess people with catheter-associated UTI if symptoms worsen at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as sepsis • previous antibiotic use, which may have led to resistant bacteria. **Referral and seeking specialist advice** 1.1.10: Refer people with catheter-associated UTI to hospital if they have any symptoms or signs suggesting a more serious illness or condition (for example, sepsis). 1.1.11: Consider referring or seeking specialist advice for people with catheter-associated UTI if they: • are significantly dehydrated or unable to take oral fluids and medicines or • are pregnant or • have a higher risk of developing complications (for example, people with known or suspected structural or functional abnormality of the genitourinary tract, or underlying disease [such as diabetes or immunosuppression]) or • have recurrent catheter-associated UTIs or • have bacteria that are resistant to oral antibiotics. **Preventing catheter-associated urinary tract infections**

Guideline	Potentially Relevant Recommendations
	1.4.1: Do not routinely offer antibiotic prophylaxis to prevent catheter-associated UTIs in people with a short-term or a long-term (indwelling or intermittent) catheter. 1.4.2: Give advice about seeking medical help if symptoms of an acute UTI develop
SIGN88 (Healthcare Improvement Scotland 2006)	• Do not rely on classical clinical symptoms or signs for predicting the likelihood of symptomatic UTI in catheterized patients. • Do not use laboratory microscopy to diagnose UTI in patients with catheters. • Do not use dipstick testing to diagnose UTI in patients with catheters. • Do not routinely prescribe antibiotic prophylaxis to prevent symptomatic UTI in patients with catheters. • In a hospital setting, when prophylaxis for catheter change is required, consider using a narrow spectrum agent such as gentamicin rather than ciprofloxacin to minimise the risk of C. difficile infection. • Change long term indwelling catheters before starting antibiotic treatment for symptomatic UTI. • Do not screen women with asymptomatic bacteriuria after short term catheterization. • Do not treat catheterized patients with asymptomatic bacteriuria with an antibiotic.
EPIC3 (Loveday et al 2014)	IVAD32: Do not routinely administer intranasal or systemic antimicrobials before insertion or during the use of an intravascular device to prevent catheter colonization or bloodstream infection. [Class A]
EAU (Bonkat et al 2021)	• Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI • Take a urine culture prior to initiating antimicrobial therapy in catheterized patients in whom the catheter has been removed. • Do not treat catheter-associated asymptomatic bacteriuria in general. • Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate). • Replace or remove the indwelling catheter before starting antimicrobial therapy. • Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.

Guideline	Potentially Relevant Recommendations
	• Do not use prophylactic antimicrobials to prevent catheter-associated UTIs. • Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. • The duration of catheterization should be minimal. • Use hydrophilic coated catheters to reduce CA-UTI. • Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterization.

It can be seen from the volume of guidelines that the management, treatment, and prevention of CAUTIs is a multifaceted process with many different elements to consider as part of care for indwelling catheters.

In standard practice in the NHS, people with indwelling catheters receive regular checks and replacement of catheters when necessary, with good hygiene practices and education for both healthcare teams and patients forming the basis of infection prevention. Clinical expert discussion indicated that initial catheterization will be done in a clinic or ward setting and each patient receives a 'catheter passport' outlining their management plan. Catheter care and regular checks are then done via a GP or district nurse. Prophylactic antibiotics are prescribed in some circumstances. However, use of prophylactic antibiotics is not routinely recommended to prevent CAUTIs in people with a short-term or a long-term (indwelling or intermittent) catheter (NICE 2018a; Healthcare Improvement Scotland 2006; Bonkat et al. 2021; Loveday et al. 2016). Clinical experts noted that antibiotic resistance is a big problem with long-term catheterization and that they would not want to use broad spectrum antibiotics in this patient group if possible (see correspondence log).

UroShield is intended for use in addition to standard care for prevention of CAUTI, it does not substantially alter the management pathway and it does not replace anything currently in the pathway. It should be noted that although the company refers to UroShield "treatment", the instructions for use provided

with the device clearly state that UroShield is not intended as a treatment for an active UTI. UroShield is a device used for prevention and is not intended for therapeutic use in people with an active infection. The company clarified that, where UroShield was being considered in people with recurrent infections, the device would not be applied until after an active infection had resolved, when a new catheter was in place.

The company submission describes the point in the clinical pathway at which a decision would be made whether or not to use UroShield as an additional infection prevention measure. Three scenarios are proposed by the company, all based on current NICE guidance, pathways, and quality standards:

a) Prevention and control of healthcare-associated infections in primary and community care – patients needing a long-term urinary catheter

b) Prevention and control of healthcare-associated infections in secondary care – patients needing a urinary catheter

c) Urinary tract infections in people aged 16 years and over – with a catheter who suffer from recurrent infections.

The first of these proposed scenarios is based on an existing care pathway outlined in NICE clinical guideline 'Healthcare-associated infections: prevention and control in primary and community care' set in *primary and community care'*, specifically where *long-term* catheterization (>28 days) is indicated (NICE 2017). The company suggests that UroShield should be considered at the 'assessment and review' stage, for those thought to be at high risk of developing CAUTI. There is an equivalent assessment stage in the *secondary care* setting, again indicating that UroShield would be considered for high risk cases if they are expected to be catheterized for more than 48 hours. The assessment and review stage in both primary and secondary care happens prior to catheter insertion. Therefore, in this approach, UroShield would be attached to the catheter at the time of insertion as a first line option to reduce the risk of developing infection.

The third scenario refers to the NICE pathway for UTIs in people aged 16 and over, so relates to patients with a catheter who have an active UTI. The company suggests that use of UroShield should be considered when deciding 'when to refer to hospital or seek specialist advice'. The proposed supporting pathway explains that UroShield would be used after confirmation of CAUTI diagnosis, in people with *recurrent infections*, defined as two or more UTIs in the past 6 months or three in one year (Bonkat et al 2021). The company propose that when an active infection has been treated, UroShield can be attached to the catheter to reduce the risk of further recurrent infections.

There is currently no agreed definition of people at 'high risk' of infection. The company proposed a number of parameters that might contribute to this consideration, including factors such as gender, previous history of urinary tract problems, neurological conditions, previous UTIs, previous and/or current abnormal voiding patterns, current catheter history, incontinence and/or co-morbid conditions such as diabetes or immunosuppression. Clinical expert input agreed that there is no standard definition for 'high risk' and that identifying any specific risk factors was difficult.

The clinical experts stated that UroShield is unlikely to be considered as a first line prophylactic option and that they would most likely use the device for patients with recurrent infections in whom other measures have failed (see correspondence log). However, they did acknowledge that certain community settings such as nursing homes or care homes might find it more beneficial. It may be less work for the carer looking after them in this setting. Home-based patients, however, may require more support from district nurses.

The company and the clinical experts agree that the benefits of UroShield are most likely to be observed in the community and primary care setting. The main target population would be those expected to require long-term catheterization, and at high-risk of CAUTI (including those who have previously experienced recurrent infections).

Special considerations, including issues related to equality

In adults, women are more likely to develop a catheter-associated urinary tract infection than men. Cerebrovascular disease and paraplegia are associated with an increasing likelihood of CAUTI. Sex and disability are protected characteristics under the Equality Act.

UTIs are an important cause of morbidity and antibiotic use in older adults. Age is a protected characteristic under the Equality Act.

The clinical experts agreed that infection risks may vary according to catheter placement (urethral or supra-pubic), biological sex, age, cardiovascular disease or paraplegia, and other parameters.

The EAC has not identified any additional equalities concerns.

4 Clinical evidence selection

4.1 Evidence search strategy and study selection

The company conducted a search encompassing the key components of the decision problem. The company study selection was made using the following criteria:

- Inclusion – use of UroShield in relevant patient population (catheterized patients).
- Exclusion – use of non-UroShield devices, use of ultrasound for imaging, histotripsy, non-human studies including in vitro laboratory studies, non-research articles (e.g. editorials, letters, comments).

The company search was conducted across 6 databases, including 2 for grey literature, and the company website, identifying (after deduplication and removal of non-English language publications) a total of 476 references. The company also searched 4 clinical trial registry platforms for ongoing studies. The database search strategies were comprehensive, using a combination of

free text terms and indexed terms. It was noted that the terms used to describe the device were broad rather than specific, and did not incorporate truncation i.e. 'surface acoustic waves' not 'surface acoustic wave*' which would fail to identify records that contained 'Surface Acoustic Wave Actuator'. The company also limited the searches to English language publications and those described as a clinical or controlled trial. As some key scope concepts had not been adequately captured, and together with the limits applied, the EAC were not confident that all relevant literature had been identified and therefore conducted their own systematic searches. Details of the company and EAC searches are provided in Appendix B. The EAC literature searches identified 21 references, these were independently screened by title and abstract in accordance with the scope by two researchers. There were no disagreements on inclusion, and all studies included by the company were eligible according to the scope. Study selection flow diagrams, outlining the number of studies excluded at each stage for both the company and EAC, are available in Appendix B.

4.2 Included and excluded studies

None of the studies identified by the company were excluded by the EAC; 8 studies (13 publications) were considered relevant to the decision problem. These are presented separately in Table 3 according to the anticipated duration of catheterization:

- 3 long term (Markowitz et al. 2018; da Silva et al 2021; Nagy et al. 2011)
- 4 short term (Ikinger et al. 2007, Shenfeld and Haris 2010, Zalut 2007, Zillich et al. 2014).
- 1 unreported duration (Turan et al. 2012)

The EAC considers the included studies to be well aligned with the decision problem, with all PICO components in the included studies considered relevant.

Table 3: Studies selected by the EAC as the evidence base

Study and type	Supporting evidence	Population	Intervention	Comparator	Outcome measures	EAC comment
Long-term catheterization (>28 days)						
Markowitz (2018) US – RCT NCT03090373	Peer-reviewed journal article (Markowitz 2018) Clinical study report Study protocol also available (US-2 Revision 2) Rosenblum (2017)	Total n=55 US study in a 'skilled nursing facility chain' with long-term indwelling urinary or suprapubic catheters (>1 year) and recently treated UTI (within 90 days). 76% male Mean age = 79.9±5.0 80% (n=44, 23 in the UroShield group and 21 in the sham group) had a urinary catheter.	n=29 UroShield attached to catheter for 30 days, followed by 60 days of standard care.	n=26 sham device attached to catheter for 30 days, followed by 60 days of standard care.	- Change in bacterial load (CFU count at baseline, 30 days, 60 days, 90 days) - Number of new infections (requiring antibiotics)	- This is a peer-reviewed study. - Relevant to scope. Low risk of bias, although there is uncertainty about between-group differences at baseline. - Subjects and investigators were blinded to treatment allocation. - Sponsored by NanoVibronix - Rosenblum (2017) confirmed by company as being the same study
da Silva (2021) UK – Before/after comparison	Peer-reviewed journal article (da Silva 2021)	Total n=23 NHS adult patients with 2 or more UTIs in the previous 6 months or 3 or more UTIs in the last 12 months and where all other options were exhausted in primary or secondary settings	n=23 UroShield	Baseline data (intra-patient before/after comparison)	- Change in number of UTIs (at baseline and final 3 weeks) - Use of antibiotics - Catheter blockage - Unplanned catheter changes - Bladder washouts - Pain score	- 80% of patients were taking antibiotics while testing the device with some patients taking long term nitrofurantoin - no reporting of demographic details and extremely limited/vague reporting of patient recruitment, previous treatments and reasons for using UroShield

Study and type	Supporting evidence	Population	Intervention	Comparator	Outcome measures	EAC comment
		Catheter duration: 5-17 weeks ('Most patients were on a trial for a period of 12 weeks') Primary or secondary care setting Note: 29 patients were recruited. Communication with the study author indicated that 2 patients passed away from other healthcare complications and four others withdrew for various medical reasons.				- Some additional details provided by the study author prior to the full study being published (see correspondence log)
Nagy (2011) Hungary Comparative case series	Conference abstract & poster	Total n=27 People requiring long-term catheterization (setting not reported) Catheter duration: =8 weeks Indication for catheters included prostate cancer, BPH, urinary incontinence, vesicoureteral reflux)	n=14 UroShield	n=13 No UroShield	- Significant bacteriuria (>100,000 CFU/ml) - Rate of biofilm formation and encrustation	- Not peer-reviewed - No description of treatment allocation criteria
Short-term catheterization (≤28 days)						

Study and type	Supporting evidence	Population	Intervention	Comparator	Outcome measures	EAC comment
Ikinger (2007) RCT – Germany	Conference poster (Ikinger 2007) Conference poster (Zillich 2008)	Total n=22 People with urological cancer Catheter duration: 5-13 days (average 9±2 days)	n=11 UroShield	n=11 sham device	- Biofilm formation (assessed using scanning electron microscopy) - Bacteriuria (not defined) - Adverse events (not detailed)	- Not peer-reviewed - Earliest clinical study of UroShield (conducted 2005-2006)
Shenfeld & Haris (2010) RCT – Israel NCT00446732	Clinical trial report, provided by the company	Total n=40 Hospitalised patients requiring urinary catheterisation Catheter duration: >24 hours, ≤13 days	n=27 UroShield Driver was replaced every 48 hours 'for charging needs'	n=13 Standard care (urinary catheter alone)	- Patient complaints (pain, discomfort, burning sensation, itching, spasm) - Bacteriuria (assessed to day 3 only) - Use of pain medication - SAEs and device-related adverse events	- Not peer-reviewed, trial - High risk of bias - Open label (unblinded) - Trial approved for n=210 but was closed early by the company - Tissue damage, catheter blockage or changes, UTIs, use of antibiotics, presence of biofilm, not evaluated due to lack of power - Potentially flawed sample-size rationale with risk of multiplicity (multiple t-tests) - Analysis assumes data are normally distributed
Zalut (2007) Case series - Location NR	Company web report	Total n=10 Discharged from ED with a urinary catheter (home care setting?) Catheter duration: 4-12 days (average 6.6 days)	n=10 UroShield	n/a	- Pain, discomfort, spasm, burning, itching - Wellbeing - Follow-up to 4 days	- Not peer-reviewed - Reported only on company website - No statistical analyses - Some conclusions not evidenced (tolerance & injuries)

Study and type	Supporting evidence	Population	Intervention	Comparator	Outcome measures	EAC comment
		No results are reported beyond day 4				
Zillich (2014) Randomised Trial – Germany	Company web report	Total n=40 Following radical prostatectomy Catheter Duration: 7-12 days (average 8.4 days for group 1; 8.3 days group 2)	n=20 UroShield + single dose Ceftriaxon	n=20 Post-operative dose of Ceftriaxon 2g on Day 1-3 + trimetoprim 2x200mg per day until the end of the study	- Bacteriuria/UTI - Antibiotic usage	- Not peer-reviewed - No statistical analyses - UTIs not reported - Unsubstantiated conclusion (superiority)
Duration Unclear						
Turan (2012) Case Series – Turkey	Turkish language report, translation provided by the company	Total n=4 Hospitalised patients requiring catheterization (no other details reported)	n=4 UroShield	n/a	No specific outcomes reported. General reports for each of the patients included in the study.	-Translation provided by company - High risk of bias - Unblinded - Very small sample size, all patients with different indications for catheterization - No statistical analysis

Abbreviations
CAUTI, catheter associated urinary tract infection; CFU, colony forming units; EAC, external assessment centre; ED, emergency department; NR, not reported; RCT, randomised controlled trial; SAE, serious adverse events; UTI, urinary tract infection

5 Clinical evidence review

5.1 Overview of methodologies of all included studies

A total of 13 publications were eligible for inclusion in this review which reported information from a total of 8 studies. It was not possible to formally appraise the quality of most of the studies due to insufficient detail about the study design and conduct. However, the EAC has included some comments relating to study quality in section 5.2. The types of available evidence are listed in table 4.

Table 4: Study types included

Type of evidence	References
Peer reviewed, published journal article	Markowitz (2018) Da Silva (2021) Turan (2012) – this paper is published in Turkish language with a translation provided by the company.
Conference abstracts and/or posters	Nagy (2011); Zillich (2008 & 2014); Ikinger (2007)
Clinical study reports	Markowitz (2018 – same study as published); Shenfeld & Haris (2010)
Company web reports	Zillich (2014 – same study as presented at conferences); Zalut (2007)
Baseline patient data submitted at EAC request	da Silva (same study as published manuscript). Additional study data was provided via e-mail (see correspondence log).

5.2 Critical appraisal of studies

Amongst the documents submitted, only three peer-reviewed publications were available (Markowitz et al. 2018; da Silva 2021; Turan et al. 2012).

Critical appraisal of Markowitz et al. (2018) indicated concerns in some domains, but an overall low risk of bias (Cochrane Risk of Bias Assessment Tool (Sterne et al. 2019), see Appendix C). Formal quality assessments were not carried out for the remaining studies as none report enough information on

methods to facilitate appraisal. However, some limitations are discussed below and recorded in Table 3.

Markowitz et al. (2018) reported data from a double-blinded, randomized-controlled trial, which compared UroShield with a sham device in selected patients from a chain of nursing homes in the USA. All patients included in the study had an indwelling urinary or suprapubic catheter for >1 year and had had a treated UTI in the 90 days leading up to study enrolment.
According to the clinical study report, the population was 76% male, with a mean age of 79.9 (±5.0) years, and around 80% had a urinary catheter (presumably the remainder had a suprapubic catheter). Baseline differences between groups were not reported. Reasons for catheterization were not provided, but all selected patients had an indwelling catheter for more than one year prior to enrolment, and a treated UTI within the previous 90 days. Patient numbers were small (with 29 of 55 patients randomised to UroShield), and statistical multiplicity may have increased the risk of a Type 1 error (where the likelihood of falsely identifying a significant finding is inflated).

Da Silva (2021) is a before and after study and critical appraisal using Joanna Briggs Institute critical appraisal checklist for case series studies (JBI) indicated some concerns around patient recruitment. The study recruited 29 patients but a complete dataset is only available for 23 of the 29 patients because 2 patients passed away from other healthcare complications and four others withdrew for various medical reasons. Patient demographic details are not reported in the publication although some additional information was provided directly to the EAC by the author (see correspondence log). Reporting of reasons for patients using UroShield is vague stating simply ‘where they had exhausted all other avenues’. The other avenues are not specified further.

Turan et al. (2012) is a Turkish language paper with a translation provided by the company. It is a narrative report on the outcomes of 4 patients who had UroShield attached to their catheters during hospital stays. The paper reports

very limited, narrative methods and results. There are no defined aims and objectives, no clearly stated outcomes and no statistical analysis.

Nagy et al. (2011) is a conference abstract and poster which reports the results of a comparator study. The sample size is small with 27 patients in total. Demographics were similar between the groups. No information is provided on how the patients were allocated to the UroShield or control group. Results were presented but the level of significance of the differences was not reported.

Iklinger et al. (2007) and Zillich et al. (2008) report the same RCT in two conference posters. Again, the sample size is small, with 22 urological cancer patients. Information on reasons for hospitalization is given but no other demographics. No details are given on method of randomization or blinding although it is stated the trial is a ‘double blind sham controlled randomised study’. Outcomes are in some cases not well defined, bacteriuria is not defined nor are adverse events.

Shenfeld and Haris (2010) is clinical trial report of an open labelled comparative randomized trial. The trial was funded by Nanovibronix. The trial was approved for 210 patients but only recruited 40 as it was closed early because the company decided to start marketing UroShield. The lower sample size meant that not all outcomes were assessed because of lack of power. The two study groups were similar in demographics. No blinding took place, so bias is a potential issue.

Zalut (2007) is very brief company web report of a case series with a sample size of 10 patients. Only age was reported and no statistical analysis was conducted, only narrative and summary quantitative data were reported.

Zillich et al (2014) is a company web report of a clinical trial, in which 40 patients were recruited, 20 to each arm. No information was provided on randomization or blinding. The age of the patients was reported. One of the

objectives (‘reduce antibiotic usage’) was not reported and no statistics were reported for the outcomes.

Overall, the EAC considers the quality of the evidence to be low. This is due to a lack of peer-reviewed publications, small study sample sizes, lack of detailed reporting of methods, outcomes measures, and results.

The EAC query why the randomized trial (Shenfeld 2010) was stopped early. Had this study completed and reported results for the planned 210 patients, this study had the potential to add valuable evidence where so little currently exists. Additional information from the company indicated that closure of the study was due to company commercial strategy and that the quoted cost for the 210 patient study could not be fully funded by the company at that time.

5.3 Results from the evidence base

There is limited clinical outcome data reported in a total of 8 studies (Markowitz et al. 2018; da Silva et al 2021; Nagy et al. 2011; Ikinger et al. 2007, Shenfeld and Haris 2010; Turan et al 2012; Zillich et al 2014).

Only one study, a before and after comparison including 46 patients, was based in the UK in a community setting and is directly relevant to the UK (da Silva et al. 2021). In all studies, the use of UroShield was prophylactic and is therefore likely to reflect how UroShield might be used in the NHS. Clinical experts indicated that UroShield would not be used as a first line option and that the benefit of UroShield is likely to be seen in patients in the community setting. Therefore, studies conducted in the community setting that included patients with previous UTI (Markowitz et al. 2018) or recurrent infections (da Silva et al. 2021) are likely to be more reflective of potential UK practice.

Reasons for catherization were poorly reported across the studies, with only studies of short-term catheterization reporting any details, perhaps reflecting the varied reasons why an indwelling catheter might be required.

None of the studies report any specific patient groups that may be more at risk of CAUTI. However, the clinical experts have indicated that defining high risk in this patient group is difficult.

The most commonly reported outcomes are bacterial load/bacteriuria (Markowitz et al. 2018; Nagy et al. 2011; Ikinger et al. 2007; Shenfeld & Haris 2010; Zillich et al. 2014) and rate of UTIs and/or antibiotics required (Markowitz et al. 2018; da Silva et al. 2021; Nagy et al. 2011; Shenfeld & Haris 2010). Other reported outcomes include catheter blockages and unplanned catheter changes (da Silva et al 2021; Nagy et al. 2011), bladder washouts (da Silva et al. 2021), biofilm formation (Nagy et al. 2011; Ikinger et al. 2007) and patient reported outcomes (da Silva et al. 2021).

Adverse events are also reported in a number of studies and these are discussed in more detail in section 6.

Long-term Catheterization

Three studies report results in people who have long-term indwelling catheters (Markowitz et al. 2018; da Silva et al. 2021; Nagy et al. 2011). Duration of long-term catheter use ranged from a minimum of 8 weeks up to more than 1 year. However, the UroShield device was used for between 30 days and 84 days (12 weeks). In Markowitz et al (2018), UroShield was used for 30 days, with a total follow up of 90 days.

Although all patients with indwelling catheters will have bacterial colonization, significant bacteriuria can result in UTIs. Poor quality evidence from 2 studies (Markowitz et al. 2018; Nagy et al. 2011) with a total of 82 patients, suggest that the addition of the UroShield device can result in lower levels of colony forming units (CFUs) compared with a sham device or no UroShield (table 5). Evidence suggest that the addition of UroShield may result in a reduction in UTIs and need for antibiotics. However, the evidence for UTIs and antibiotic use is limited and poor quality.

Catheter blockages and unplanned catheter changes were significantly reduced following the addition of UroShield to the catheter (da Silva et al. 2021). Premature catheter removal rates did not differ between patients with or without UroShield (Nagy et al. 2011) suggesting that UroShield is safe and tolerated by patients.

Bacterial Load/Bacteriuria

Markowitz et al. (2018) compared UroShield with a sham device where baseline CFUs for all groups were 100k (100,000) or greater. They reported that after 30 days there was a significant improvement in CFU rates compared with baseline in the UroShield group, but no improvement in the sham device group. When compared with sham device, UroShield showed a mean improvement advantage from baseline to 30 days of 87.2k CFU ($p<0.001$). Even after UroShield was stopped at 30 days, there was a minimal increase in CFU count at both 60 and 90 days.

A second study (Nagy et al. 2011) compared the addition of UroShield to standard catheter practice and reported that, at 8 weeks, 33% (4/12) of patients in the UroShield group had significant bacteriuria (>100k CFU) compared with 82% (9/11) in the group without UroShield.

UTIs and/or antibiotic use

Markowitz et al. (2018) reported no new infections (among 29 patients) requiring antibiotics at 30 days with UroShield, compared with 7 (among 26 patients) in the sham device group. At 90 days, the rate of infection was 10% (3/29) in the UroShield group compared with 54% (14/26) in the sham device group. It should be noted that UroShield/sham devices were only used for the first 30 days.

Da Silva et al. (2021) reports a reduction in mean number of UTIs from baseline to study end; from 3.24 (SD±3.42) to 0.5 (SD±0.91).

Nagy et al. (2011) reported no difference in the rate of symptomatic UTI's between patients with and without UroShield, with none reported in either group. This was despite 4 patients in the UroShield group and 9 in the comparator group having significant bacteriuria.

Catheter Blockages, unplanned catheter changes, premature catheter removal

One study (da Silva et al. 2021) reported a reduction in mean rate of catheter blockages from baseline to study end following the addition of UroShield (2.59 SD±3.75 vs. 0.36 SD±0.9; p=0.006), as well as a mean reduction in unplanned catheter changes (2.91 SD±3.57 vs. 0.32 ±0.48; p=0.001).

Table 5: Clinical Outcomes with long-term catheterization (>28 days)

Study	Bacterial load/ bacteriuria	UTIs/antibiotics required	Catheter blockages & Unplanned changes	Bladder washouts
Markowitz (2018)	**Baseline CFUs for all groups were 100k or greater.** • Compared to baseline, the UroShield group showed significant improvement at 30 days • In the sham group CFU counts remained at 100K for each subsequent assessment (30, 60, and 90 days) **UroShield versus sham:** • Mean improvement advantage baseline to 30 days = 87.2k CFU, t (53) 18.1, p<0.001 • Mean improvement advantage baseline to 60 days = 87.5K CFU, (t (53) 18.1, p<0.001) • Mean improvement advantage baseline to 90 days = 79.3k CFU, t (53) 12.4, p<0.001 **Following UroShield Cessation** • Minimal increase in CFU count at both 60 and 90 days • No statistical difference in the decrease of CFU count from 30 to 60 days after treatment, t (28) =1. P=0.326 • Increase in CFU from 60 to 90 days for the active group (28) =1.7 p= 0.09	**New UTIs requiring antibiotics within 30 days** Intervention (UroShield) = 0/29 Comparator (sham) = 7/26 **New UTIs requiring antibiotics within 90 days** Intervention (UroShield) = 3/29 (10%) Comparator (sham Device) = 14/26 (54%) p=0.001 **Urinary vs. Suprapubic** • No treated infections for either urinary or suprapubic catheters in the UroShield group at 30 days. • At 90 days after treatment, the patients with urinary catheters had fewer treated infections compared to the suprapubic catheter (4.3% vs 33.3%, p=0.074).		

Study	Bacterial load/ bacteriuria	UTIs/antibiotics required	Catheter blockages & Unplanned changes	Bladder washouts
da Silva (2021) 'Study end result taken from final 3 weeks Comparator is baseline data from the same patients		**Number of UTIs mean (SD)** Baseline (n=21) = 3.24±3.42 Study end (n=22) = 0.5±0.91 p=0.001 **Required antibiotics** Baseline (n=22) = 2.05±2.33 Study end (n=22) = 0.77±1.11 p=0.009	**Blockages mean (SD)** Baseline (n=22) = 2.59±3.75 Study end (n=22) = 0.36±0.90 p=0.006 **Unplanned catheter changes** Baseline (n=22) = 2.91±3.57 Study end (n=22) = 0.32±0.48 p=0.001	**mean (SD)** Baseline (n=17)= 2.71±6.01 Study end (n=17)= 0.65±1.69 p=0.104
Nagy (2011)	**Significant bacteriuria (>100,000 CFU) at 8 weeks** UroShield = 4/12 (33%) No UroShield = 9/11 (82%)	**Symptomatic UTIs** UroShield = 0/14 (0%) No UroShield = 0/13 (0%)	**Premature catheter removal** UroShield = 2/14 (14%) (1 blockage, 1 bleeding) No UroShield = 2/13 (15%) (1 balloon error, 1 bleeding)	

Short-term Catheterization

Three studies report limited clinical outcomes for people with short term catheters (Ikinger et al. 2007; Shenfeld & Haris 2010; Zillich et al. 2014) and in one study (Turan et al. 2012) it is not clear whether people had long or short-term catheters or a mix (table 6).

Duration of short-term catheterization ranged from 24 hours to 13 days and all were in a hospital setting.

The evidence for UroShield in short-term catherization is extremely limited and very poor quality. None of the studies are peer-reviewed publications and one trial which intended to recruit more than 200 patients (Shenfeld & Haris 2010) was terminated early with only 40 patients recruited.

Bacterial Load/Bacteriuria

No significant difference in bacteriuria was observed in one study comparing UroShield with sham device (Ikinger et al. 2007) or another comparing UroShield plus standard care with standard care alone (Shenfeld & Haris 2010). In one study comparing UroShield and antibiotics, 5% of patients in the UroShield group had bacteriuria compared with 20% in antibiotics group (Zillich et al, 2014).

Biofilm formation

One study reported that 64% of catheters with a sham device had biofilm formation compared with 0% of catheters with the UroShield device (Ikinger et al. 2007).

Table 6: Clinical Outcomes with short term catheterization (≤28 days)

Study	Bacterial load/ bacteriuria	Biofilm formation
Ikinger (2007)	'No statistical significance was found with respect to bacteriuria'	**Biofilm on SEM** UroShield = 0/11 (0%) sham = 7/11 (64%)

Study	Bacterial load/ bacteriuria	Biofilm formation
Shenfeld & Haris (2010)	**Day 3 bacteriuria** UroShield = 1/19 (5%) No UroShield = 1/10 (10%) p=0.33 (but underpowered)	
Turan (2012)	No growth detected on urine cultures following addition of UroShield in 3/4 patients.	
Zillich (2014)	**Bacteriuria (>1,000 CFU/ml)** Intervention = 1/20 (5%) Comparator = 4/20 (20%)	

Patient Reported Outcomes

Patient reported outcomes were reported narratively in 1 study (da Silva et al. 2021). Following introduction of UroShield, all patients who responded indicated that the device was easy to use and felt that the device benefitted them. Fifty percent of patients reported feeling happier about their urinary catheter and no-one reported feeling worse. Nine patients (41%) were able to do more things with their life as a result of using UroShield. In a thematic analysis, two key themes were identified:

- Positive outcomes related to a change in well-being or to the design of the device
- Device issues as a result of patients' other conditions or minor inconveniences.

Positive Outcomes

Based on patient reports during the 12-week trial, UroShield appears to reduce the risk and frequency of CAUTIs and extend the time between catheter changes:

> *'This is now longest period I have had without getting an infection (for over 4 years).'*
>
> *'Huge success! In nearly 7 years, this is the first time able to go a month before needing catheter changes! Thank you!'*

‘The overall effect whist not being black and white immediately is the feeling of general improvement and the life of this particular catheter has been extended by at least one week on this occasion resulting in longer periods between changes.’

There also appears to be a positive impact on quality of life, with patients reporting they became more social and independent and less concerned about their condition.

‘So happy I have got the Uroshield again. Since the first trial finished and I no longer had the device my catheter was constantly blocking. Having the Uroshield has changed my life!’

Some patients reported minor inconveniences such as sediment build up in the catheter although felt that UroShield prevented full blockages and catheter changes.

In relation to the design of the device specifically, patients were broadly positive in their feedback although there were some more negative comments around factors such as battery life and not knowing how much battery life was remaining. There were also comments suggesting that the device could be uncomfortable to use at night.

6 Adverse events

The company submission included searched of MHRA, FDA MAUDE and TGA databases for any reports of device related adverse events. The EAC conducted similar searches.

No device-related adverse events were identified by the company or the EAC. Adverse events were reported in 6 of the included studies; 3 long-term catheterization studies (da Silva et al. 2021; Nagy et al. 2011) and 3 short-term catheterization studies (Ikinger et al. 2007; Shenfeld and Haris 2010; Zalut 2007). The most commonly reported adverse events in the literature were pain and discomfort. Three studies reported less pain with UroShield compared with standard care. Details of adverse events reported in the literature are reported in table 7.

The EAC note that the adverse events reported in the literature may not be directly related to the UroShield device itself but rather to the fact that using the UroShield device may reduce CAUTIs, symptoms of which can be pain and discomfort.

Table 7: Adverse Events

Study	Adverse events (non-specific)	Pain	Discomfort	Spasm	Other
Long-term catheterization (>28 days)					
da Silva et al (2021)	N/R	Reduction in mean pain scores from baseline to study end following addition of UroShield 3.30±2.23 reduced to 2.60±1.86 (p=0.017)	N/R	N/R	N/R

Study	Adverse events (non-specific)	Pain	Discomfort	Spasm	Other
Nagy (2011)	N/R	N/R	**Catheter-related complaints (score 1 to 10)** UroShield: decreased by 1.6 (from 2.6 to 1.0) No UroShield: increased by 1.3 (from 2.1 to 3.4)	N/R	N/R
Short-term catheterization (≤28 days)					
Ikinger (2007)	'No difference in reported adverse events between the two groups'	N/R	N/R	N/R	N/R
Shenfeld & Haris (2010)	**Adverse events** UroShield: 8/27 (30%) No UroShield: 10/13 (77%) **SAEs** UroShield: 0/27 (0%) No UroShield: 1/13 (8%). All AEs were unrelated to device.	**Mean ± SD (Scale 0 to 10)** **Pain score** UroShield: 2.2±2.7 No UroShield: 3.2±2.7 p=0.02 **Use of pain medication** UroShield: 17/27 (63%) No UroShield: 11/13 (85%) Similar strength.	**Mean ± SD (Scale 0 to 10)** UroShield: 2.8±3.0 No UroShield: 4.0±3.3 p=0.01	**Mean ± SD (Scale 0 to 10)** UroShield: 2.5±2.7 No UroShield: 3.6±3.2 p=0.01	N/R
Zalut (2007)	N/R	**Pain** Baseline = 6.1 UroShield (day 4) = 1.8	**Itching** Baseline = 2.6 UroShield (day 4) = 0.4 **Burning** Baseline = 3.7 UroShield (day 4) = 0.2	**Spasm** Baseline = 3.7 UroShield (day 4) = 1.0	**Wellbeing** Baseline = 3.3- UroShield (day 4) = 7.0

Abbreviations: AE, adverse event; NR, not reported; SAE, serious adverse event; SD, standard deviation

7 Evidence synthesis and meta-analysis

The company submission included a meta-analysis based on data from 4 studies (Nagy et al. 2011; Markowitz et al. 2018; Shenfeld and Haris 2010; Zillich et al. 2014). The company claims that the main strength of the clinical evidence lies in there being equivalent outcomes. Due to the limited data available, only one outcome measure contributed to the meta-analyses: "significant bacteriuria" which was defined as a count of >10k colony-forming units (CFUs) per ml.

The data from each study that were included in the meta-analysis are detailed in table 8.

Table 8: Summary of study data used in meta-analysis in the company submission

				Significant bacterial infection			
Study	**Category**	**Setting**	**Indication(s)**	**UroShield**	**Comparator**	**Total sample**	**Approx. date measured**
Nagy (2011)	Long-term	NR	Prostate cancer; BPH; urinary incontinence; VUR	4/12 (33%)	9/11 (81%)	n=23	8 weeks
Markowitz (2018)	Long-term	Nursing homes	NR	0/29 (0%)	7/26 (27%)	n=55	30 days
Shenfeld & Haris (2010)	Short-term	Hospital	NR	1/19 (5%)	1/10 (10%)	n=40	3 days
Zillich (2014)	Short-term	NR	Following radical prostatectomy	1/20 (5%)	4/20 (20%)	n=40	8 days

Abbreviations: NR, not reported; VUR, vesicoureteral reflux

The EAC agrees with the studies included in the meta-analysis and has not added any more data. Consideration should however be given to the individual study data quality and the potential impact on the usefulness of the meta-analysis result. Specific concerns identified by the EAC include:

- According to the study design, all patients recruited by Shenfeld & Haris (2010) and Markowitz et al. (2018) had a significant bacteriuria at the start of the study. This may be inconsistent with advice from the company that UroShield should not be initiated when a patient has an active urinary tract infection. However, the EAC acknowledges that bacteriuria is a proxy measure for CAUTIs and may not always be associated with symptomatic UTI requiring treatment.

- Shenfeld & Haris (2010) reported bacteriuria for 43 patients on day 0 (although they report having recruited only 40 patients), and on day 3 only reported findings for a total of 29 patients (a loss of at least 11 patients). The authors do acknowledge that this measure is underpowered.

- Markowitz et al. (2018) reports infection rates at 30 days and 90 days and the company state they have used the 30-day result to reduce heterogeneity in follow-up times (for comparison, the rates at 90 days were 3/29 with UroShield and 14/26 with SoC). The study methodology report however that UroShield was used for the first 30 days and was then followed by standard care for 60 days. So using the data for 90 days would not reflect UroShield use, where the device must remain attached at all times. The EAC suggest that only the 30-day UroShield data is used.

The company meta-analysis was performed using STATA and the results were verified by the EAC using Cochrane Review Manager (Cochrane Collaboration 2014). The company applied a fixed effect, Mantel-Haenszel model. The Mantel-Haenszel model is relatively robust when study size is small and/or event rates are low. If the association is slight but consistent across the tables, this procedure will be effective in detecting that association (Kuritz et al. 1988).

Results from the company meta-analysis report a pooled risk ratio of 0.25 (95% CI 0.11-0.57; I^2=0%) indicating a potential 75% reduction in significant

bacterial infection with UroShield compared with standard care. The EAC agrees with the studies included and the methodological approach to the meta-analysis. The EAC pooled risk ratio is 0.27 (0.12-0.57; I^2=0%) (see table 9 and figure 1 and figure 2 for detailed comparison). For information, using the 90-day infection data from Markowitz 2018 results in risk ratios of 0.28 (0.15-0.54).

Table 9: Meta-analysis results comparison

Study	Company Result Risk Ratio (95% CI)	EAC Result Risk Ratio (95% CI)
Markowitz	0.06 (0.00 – 1.00)	0.06 (0.00 – 1.00)
Nagy	0.41 (0.17-1.02)	0.41 (0.17-0.95)
Shenfeld	0.53 (0.04-7.55)	0.53 (0.04-7.55)
Zillich	0.25 (0.03 – 2.05)	0.25 (0.03 – 2.05)
Pooled Result	**0.25 (0.11 – 0.57)**	**0.27 (0.12-0.57)**

Figure 1: Results of company meta-analysis using STATA (taken from company submission)

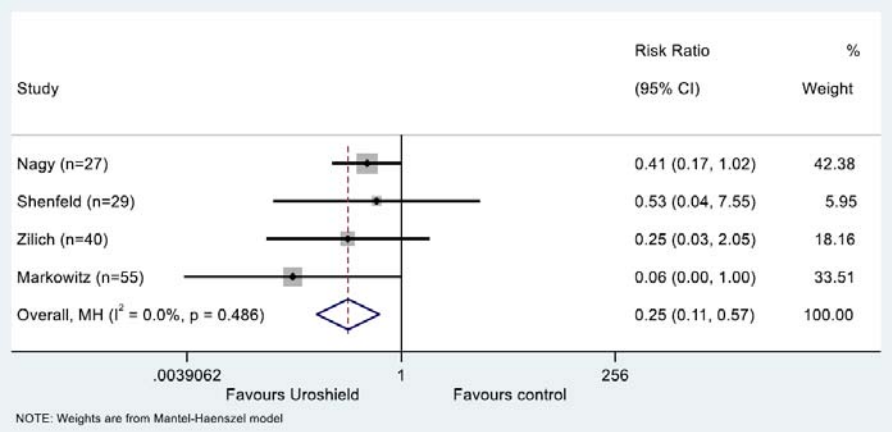
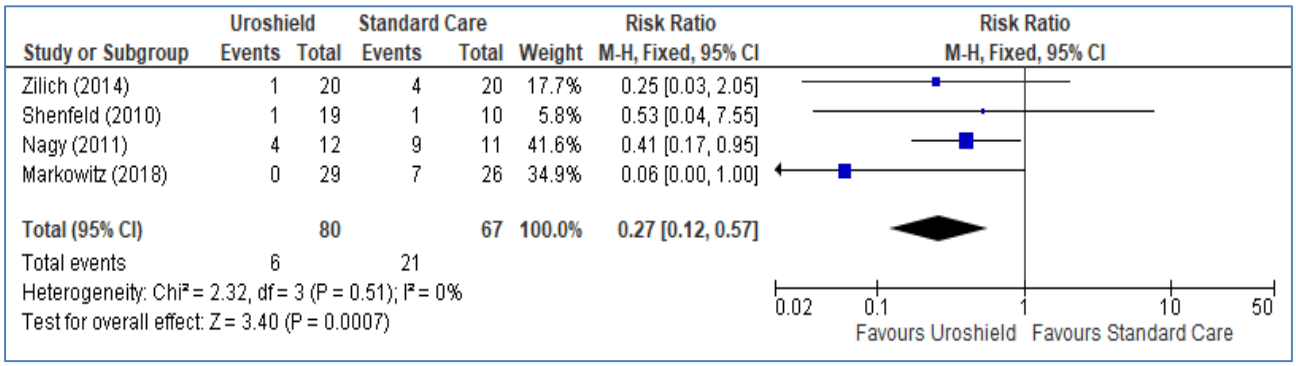


Figure 2: EAC meta-analysis using RevMan v5.3 (Cochrane)



Overall, there are limited published, peer-reviewed studies available (1 peer-reviewed publication, 1 clinical trial report, 1 company web report/poster, 1 poster). The studies vary in their settings, follow-up times and reasons for catheterization. The EAC therefore advise that the committee consider carefully the extent to which the results of the meta-analysis can be considered generalisable to the wider population particularly as the results of the meta-analysis are being used in the economic analysis.

Although there are some concerns around the quality of the data driving the meta-analysis, the EAC note that the result indicates that the use of UroShield has a significant impact on the occurrence of bacteriuria and currently there are no better data available from any of the individual studies.

8 Interpretation of the clinical evidence

The current evidence suggests that using the UroShield device may reduce the risk of bacteriuria and symptomatic UTIs. However, the clinical evidence supporting the company submission is limited in both quantity and quality at this time. Only two studies have been published in a peer-reviewed journal, and key study design details are omitted from other evidence sources. One trial which had planned to recruit more than 200 patients was terminated early.

Although the company has attempted to pool outcomes by conducting meta-analyses, there are concerns about both the robustness of the evidence from

the individual studies and the usefulness of bacteriuria as a proxy measure for infection. The only UK study report submitted by the company (da Silva et al 2021) was not included in the meta-analyses as it did not report rates of bacteriuria. However, the use of UroShield was prophylactic in all studies and is therefore likely to reflect how UroShield might be used in the NHS. As the clinical experts indicated that UroShield would not be used as a first line option and that the benefit of UroShield is likely to be seen in patients in the community setting, the EAC considers that studies conducted in the community setting which included patients with previous UTI (Markowitz et al. 2018) or recurrent infections (da Silva et al. 2021) are likely to be most reflective of potential UK practice.

Patient feedback on their experiences of using the device appear to be largely positive, with patients reporting that using UroShield resulted in a reduction in infections and a longer duration between catheter changes. People using the UroShield device reported that their quality of life improved as a result. There were some negative comments, primarily around the fact that the device could be uncomfortable to sleep with and that the battery life was short, with no way to tell how much battery was left.

8.1 Integration into the NHS

UroShield is currently in use in approximately 7 NHS trusts in England. However, data were only submitted to NICE from one small unpublished UK study, with limited information about the selected population (n=23, da Silva et al. 2021).

Adoption of the technology would not require a significant change in current NHS care pathways, as it is an adjunct to existing infection prevention measures. The device is relatively simple to operate and little time would be required for training and implementation. Patients, carers and healthcare staff (predominantly district nurses) are provided with training in how to use UroShield, supplemented by a written quick start guide and instructions for use. The company state that training takes up to 30 minutes for clinicians and 10 minutes for patients and all training content is included with the instructions

for use. The company are also currently developing a video to support remote training for staff.

UroShield must be used continually to be effective in preventing biofilm formation. As the battery life is 6 hours when fully charged, most users will connect the driver to a mains power source overnight. The majority of people who might be considered eligible for UroShield are not likely to be very mobile. Those with capacity may also be experienced in managing their indwelling catheter. Clinical experts have suggested that patients would be highly motivated to prevent CAUTIs, and therefore willing to tolerate any possible inconvenience associated with running the device. Compliance in one UK study (da Silva et al. 2021) was good with 23/29 participants using the device for the full study period. Clinical expert input also suggests that compliance would not be a problem as this is a patient group who are desperate for a solution and for improvement in their quality of life.

There is a chance that the device battery could run out if the user was away from a charging source for more than 6 hours. The company indicated that short periods of a few minutes of disconnection would not be expected to have a detrimental impact on the effectiveness of the device. However, this has not been assessed in any studies and the company does not recommend the device be disconnected.

8.2 Ongoing studies

The EAC searched the Clinical Trials.gov and EU-CTR registries for relevant ongoing trials.

The EAC identified one research project currently ongoing in the UK which is funded by Nanovibronix and the national Biofilms Innovation Centre. The research project comprises three separate studies:

- Controlled laboratory assessment on the effects on catheter biofilms using an artificial bladder model system.

- A patient study using a combination of culture-based, imaging, and 16S RNA sequencing techniques to study microbial diversity and abundance pre- and post-UroShield in long-term indwelling catheter users.

- Qualitative assessment on the use of the UroShield.

The study aims to evaluate how Surface Acoustic Wave Therapy affects bacterial colonization and community structure on long term indwelling urinary catheterization. It will assess any changes to the catheter-associated microbiome in order to understand the impact of the Nanovibronix UroShield on the biofilm community. In addition, validated questionnaires and in-depth one-to-one interviews will be used to understand the participant's experience of using UroShield.

One ongoing trial, based in Canada, was also identified by the EAC (NCT03785262). The study is a randomized controlled trial comparing UroShield and a sham device for the prevention of urinary tract infections in 24 patients (table 10).

Table 10: Summary details for ongoing studies

Trial Identifier	Study Design	Population	Outcome	Current Status
NIHR UK To evaluate the effect of surface acoustic wave ultrasound on the formation of biofilm and the presence of bacterial uropathogens on urinary catheters.	Observational Study (laboratory and interview) to evaluate the effectiveness and safety of the NanoVibronix UroShield™ plus standard therapy under conditions of intended use 16 weeks duration	N=30 patients with indwelling catheters who suffer from repeated UTIs and catheter blockage	• Laboratory measurement of bacterial colonisation of the urinary bladder • Quality of life issues described by the participants after using the UroShield • Frequency and severity of catheter-related adverse events before and during use	Active Planned duration: May to August 2021
NCT03785262 Canada Low Energy Surface Waves for Neurogenic Bladder Patients With Indwelling Catheters	Randomized Controlled trial comparing UroShield with sham device for prevention of urinary tract infections	N=24 participants **Inclusion Criteria:** • >18 years of age • Spinal cord injury (>1 year), multiple sclerosis (>1 year), spina bifida, Parkinson's (>1 year) • Indwelling catheter (urethral or suprapubic) for >3 months, and used as primary bladder management mechanism • >1 urinary tract infection in the last 12 months **Exclusion Criteria:** • Intravesical Botox in the last 6 months • Chronic antibiotic suppressive therapy • Active symptomatic UTI on day of randomization • Unable to understand written and spoken English • Prior/current utilization of the Uroshield device	• Bacteriuria • Neurogenic bladder symptom score • Sediment/debris at end of 30 days • Microbiome comparison of biofilms • Scanning electron microscopy of biofilm	Estimated Study completion is February 2021 No results yet posted.

9 Economic evidence

9.1 Published economic evidence

Search strategy and selection

The company conducted a search encompassing the key components of the decision problem. The search was conducted across 4 databases identifying (after deduplication and removal of non-English language publications) a total of 67 references. The database search strategies were comprehensive using a combination of free text terms and indexed terms, it was noted that the terms used to describe the device were broad rather than specific and did not incorporate truncation i.e. 'surface acoustic waves' not 'surface acoustic wave*' which would fail to identify records that contained 'Surface Acoustic Wave Actuator'. The company limited the searches to English language publications and applied appropriate terms to limit to economic evidence. The company did not identify any publications that were considered relevant for inclusion.

To ensure that all relevant and recent literature had been identified, the EAC conducted their own combined systematic searches for both clinical and economic evidence, no additional evidence was identified for inclusion. Details of the company and EAC searches are provided in appendix A.

Published economic evidence review

No published economic evidence relating to UroShield was identified.

Results from the economic evidence

No published economic evidence relating to UroShield was identified.

9.2 Company de novo cost analysis

Economic model structure

The model was a simple decision tree, with a variable time horizon depending on the setting selected. The settings presented were:

- All hospital patients
- Hospital with catheterization ≤28 days (short-term)
- Hospital with catheterization >28 days (long-term)
- ICU setting
- All community patients
- Community patients with recurrent UTI

These populations do not necessarily match those identified in the clinical literature. Different definitions are used for short and long term catheterization. However, Nagy et al. (2011) and Markowitz et al. (2018) both have populations consistent with >28 day durations (Markowitz setting is in nursing homes), and Shenfeld & Haris (2010) and Zillich et al. (2014) have populations consistent with <28 day durations (both in hospital settings). There was no evidence identified to support the ICU or recurrent community settings although da Silva at al. (2021) was patients with repeated UTI.

Hospital settings had a time horizon of the duration of catheterization or the duration of treatment for a CAUTI. Community settings had a time horizon of 30 days, or the duration of treatment for any CAUTI. Both costs and benefits remain the same per month, and this is therefore presented as a rolling 30-day model. The costs of initial catheterizations are not included in the model as these are considered to be the same in both arms. The perspective is NHS, and no discounting is applied. The EAC consider the structure and perspective to be appropriate.

In all settings UroShield is considered as an addition to standard of care (SOC). Therefore, the model structure is identical in both the intervention and comparator arms, and therefore, only one arm is presented in the model diagrams below (Figure 3 and Figure 4). The EAC believe that the model

structure for community patients in the written submission does not accurately represent the data or model used. CG139 is used as the basis for much of the community modelling. In CG139, patients may transition from CAUTI 1st line treatment directly to:

- 1st line failure (8%), OR
- MDR (6%), OR
- CABSI (3.6%), OR
- Cure.

In the UroShield model as submitted in Excel, the transitions are from CAUTI treatment to:

- 1st line failure (2nd line treatment), then TO MDR, OR
- CABSI, OR
- Cure.

I.e. patients transition to MDR following 1st line failure (2nd line treatment). In the company's written submission, the model structure shows CABSI can only develop from an MDR infection. However, both CG139 and Smith et al (2019), on which the model is based, report CABSI as a proportion of total CAUTI treated, not as subsequent to treatment failure. Therefore, using these values from these reports, CABSI should be considered as independent of these proportions. Figure 4 shows the model structure according to the Excel model and data included, as understood by the EAC. Note, that this difference is entirely conceptual and has not altered the actual model.

Patients in all settings get a CAUTI in accordance with the risk in the model. The technology costs of implementing UroShield are balanced against the savings from the CAUTIs prevented in the intervention arm. In the hospital setting, the treatment costs for CAUTI are limited to the hospital stay and the

infection is considered to be resolved during that stay. In the community setting, the treatment costs are limited to the duration of treatment for that infection. In all settings, CAUTI may lead to bacteraemia (catheter acquired blood stream infection, CABSI). Death from CABSI is only included in the model to determine the number needed to treat (NNT) to avoid one death. In the hospital settings, treatment for CAUTI (without CABSI) is costed as a single intervention, whereas in the community this is broken down into first line treatment, second line (where initial antibiotics fail), and multi-drug resistant (MDR) infections.

Figure 3: Hospital setting, model diagram (showing single arm only)

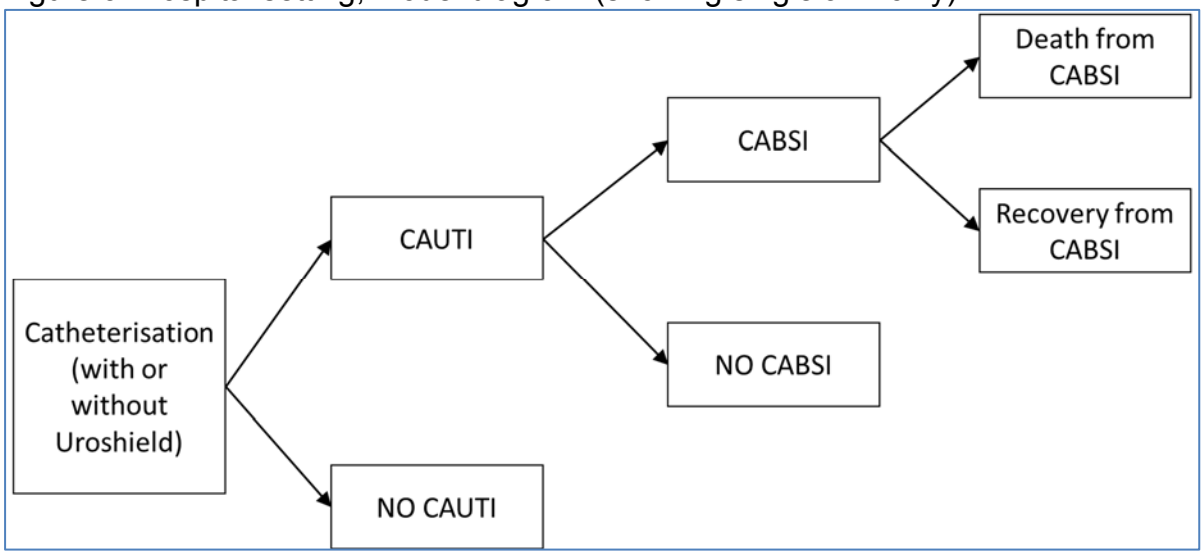
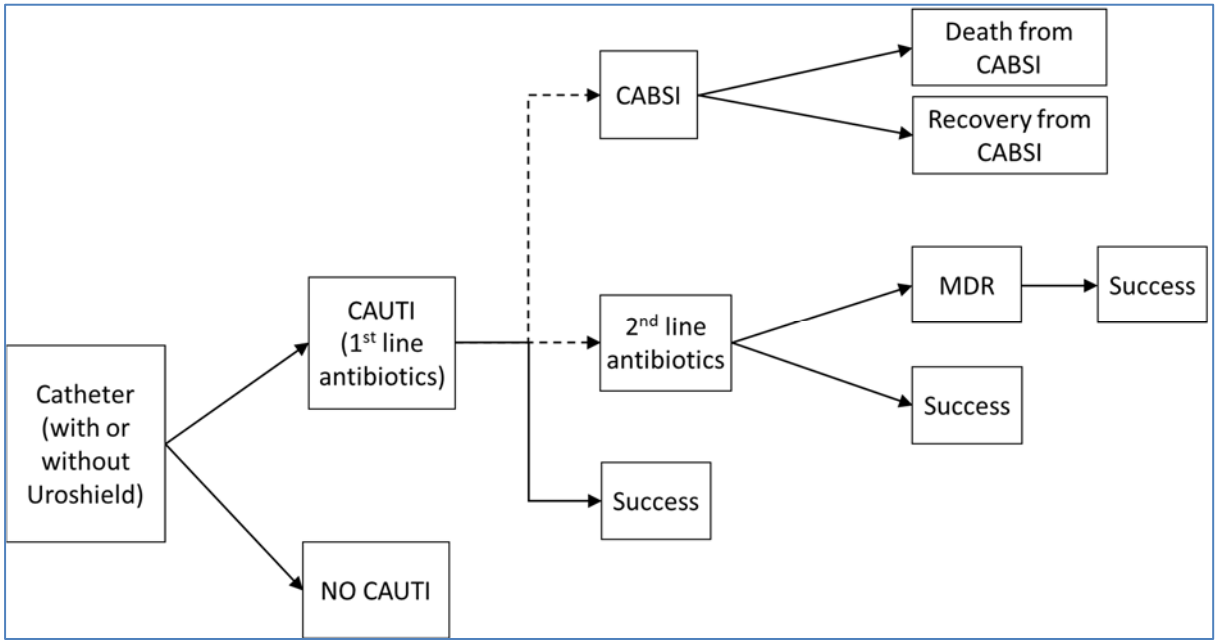


Figure 4: Community setting, EAC model diagram (showing single arm only)



The company included a number of assumptions in the model and the EAC identified a number of additional assumptions (table 11).

Table 11: Assumptions identified by the company and the EAC include:

Assumption	Justification / source	EAC comment
Short term catheterization is ≤28 days	In line with EPIC 3 (Lovejoy 2014)	Accepted by EAC
The UroShield driver has a two-year life-span and each driver can be re-used for an individual patient or for different patients.	In line with warranty provided for device. (NanoVibronix)	Accepted by EAC, however the calculation assumes that the driver is used for every day of its 2 year life span. The EAC changed this to 80% usage.
Each UroShield actuator has a life-span of 30 days. The actuator is replaced on the existing catheter every 30 days.	In line with product information. (NanoVibronix)	Accepted by EAC
There are no training costs in the model and no nursing time has been included for connecting the driver and attaching the actuator when inserting a new catheter.	The UroShield driver connects to existing catheters with no significant training required. The time to attach the driver and replace the actuator when necessary is negligible.	The costs of inserting and maintenance of the catheter are therefore not included in the model, as they are the same in both arms. Accepted by EAC, and in line with expert advice.
The efficacy of UroShield in preventing CAUTI is the same regardless of setting.	The mode of action of UroShield is such that efficacy should be independent of setting (acute, ICU or community).	This is based on a meta-analysis which includes different settings and populations.
Additional assumptions identified by EAC		
There are no long-term cost consequences to CAUTI or CABSI	Models have short time horizons focusing on duration of catheterization in hospital, or 30 days (plus CAUTI treatment) in the community. Accepted by EAC	
There are no costs incurred by death	Deaths are calculated by the model, but no costs are incurred. Deaths are only included to determine the NNT to avoid one death. The EAC accept this is reasonable within the model presented	
The reduction in significant bacteriuria due to UroShield reported in the meta-analysis can be extrapolated to symptomatic CAUTI requiring treatment	Bacteriuria can be present without producing symptoms or requiring treatment. However, due to variations in definition and treatment thresholds for UTI bacterial load is easier to report in trials. It is logical to assume that a reduction in urological bacterial load would translate to a reduction in CAUTI risk/incidence. Accepted by EAC.	

Assumption	Justification / source	EAC comment
The definition of 'recurrent' UTIs in community patients can be applied to CAUTIs	This is based on the European Association of Urology (EAU) guidelines that define recurrent UTIs as 3 UTIs in 12 months, or 2 in 6 months. The EAC accept this assumption as patients included in the community setting may have long term catheterization.	
The efficacy of UroShield is the same for first CAUTI or recurrent CAUTI	The EAC accept this assumption as there are no data to suggest otherwise. The company refer to data suggesting that patients with recurrent CAUTI may have greater treatment needs.	
The risk of CAUTI increases linearly with duration of catheterizations.	Accepted by the EAC. It is generally accepted that risk of CAUTI increases with duration of catheterizations. EPIC3 guidelines report the risk of bacteriuria increases by 5% per day (Loveday et al 2014).	
Patients acquiring CAUTI in hospital only incur hospital costs during the index admission and are therefore cured before discharge.	There is little recent UK data to contradict this. This is also the methodology of Smith et al (2019).	

Economic model parameters

The clinical parameters and cost inputs included in the model have been checked and validated by the EAC (table 12).

Clinical parameters and variables

The key clinical parameters are the base rate of CAUTI and the reduction of this by the use of UroShield.

Hospital Infections

The base rate for hospital infections is derived from a large UK study (Smith et al. 2019) using retrospective routine data (Hospital Episode Statistics, Public Health England data, and NHS Safety Thermometer). The authors derive a mean risk of 3.8% for a catheterized patient developing symptomatic CAUTI during their hospital stay. They further report the risk at 2 days (3.1%) after catheterizations, and for durations of 40 days or longer (13.2%). The company have chosen to separate catherization duration into ≤28 days (short-term) and >28 days (long-term), based on the definition of short term catherization in the EPIC3 guidelines (Loveday 2014).

To determine a single value for the risk of CAUTI in each of the short- and long-term populations the company chose mean durations of 7 days and 42 days respectively and determined CAUTI risks based on these durations. Seven days was chosen for the short-term population based on an HTA by Pickard et al (2012). In this study, in patients who were expected to have a catheter for less than 14 days (at the point of catheterizations), there was a mean catheterization duration of just under 3 days. For the short-term population (≤28 days duration), the company considered 7 days as a reasonable estimate of the mean. For the long-term population (>28 days), the company chose 42 days as the mean duration in order to ensure that a minimum of 2 UroShield actuators were required. The duration for the overall hospital population was chosen to be 10 days, based on increasing the values reported in Pickard et al (2012).

Recent data on the duration of catheterizations in UK hospitals has not been identified. There are other interventions across health and care settings that are intended to reduce the incidence of CAUTI, such as reducing the number and duration of urinary catheters used (Loveday 2014). The unknown use and effect of these mean that only recent data would be more reliable than the estimates provided by the company. In addition, the durations of catheterizations are only used to determine point estimates of the risk of CAUTI and the technology costs for UroShield.

In the results from Smith et al (2019) the company further assumed a mean duration of 60 days catheterizations for patients in the ≥40 days category. The risk of developing CAUTI was therefore 3.1% at 2 days and 13.2% at 60 days This was linearly interpolated to determine a risk at 42 days of 10.1%. The risk at 7 days was determined as the mid-point between the risk at 2 days (3.1%) and the overall risk for the whole population of 3.8%, giving a value of 3.45%.

In the absence of other data, the EAC considers this reasonable. Both the risk of CAUTI and the technology costs are explored in the sensitivity analysis.

Community Infections

The base rate for community infections is taken from a UK survey conducted across 3 primary care trusts in October 2004 (Getliffe and Newton, 2006). The company admit that this source is outdated but that more recent data is not available. The EAC have also not been able to identify any UK data that is more recent. The authors identified the number of patients with a long-term catheter (>14 days) across community settings (GP practices, community hospitals, nursing homes) in 3 primary Care Trusts in England during October 2004. The mean rate of CAUTI in 129 catheterized patients was 8.5% in a month, with values ranging from 5% treated by district nurses, to 30% in nursing homes. NICE guideline CG139 (2017) "Healthcare-associated infections: prevention and control in primary and community care" includes a cost analysis from 2012 (Appendix J). This reports a rate of CAUTI in patients conducting intermittent self-catheterizations (ISC) of 1.14 per year. In comparison, the Getliffe and Newton (2006) rate converts to 1.02 infections per year. The EAC accepts the base case estimate for CAUTI in the community, but have increased the sensitivity range to account for the values across different setting given in Getliffe and Newton (2006).

In the recurrent population, the risk is for a patient with a long-term catheter, who gets recurrent infections, of having an infection in any given month. The European Association of Urologists' definition of a recurrent UTI is used by the company, which is 3 in a year or 2 in 6 months (Bonkat et al 2021). In this case, the population is those patients who are defined as already having recurrent CAUTI. The company suggest that patients with recurrent infections are more likely to require more intensive treatment, but have applied the same treatment costs to all community CAUTIs. The EAC could not identify any data about the epidemiology of recurrent CAUTIs in the UK.

Effectiveness of UroShield

The risk ratio for CAUTI from using UroShield is taken from the meta-analysis for bacteriuria reported in the clinical evidence. The overall value of 0.252 is applied across all populations modelled. The company also separated the

meta-analysis into 2 subpopulations based on duration of catheter use. In studies in longer-term duration the risk ratio was slightly lower (0.230), and slightly higher for short-term durations (0.318). However, the company indicate that these pair-wise analyses should be used with caution due to significant methodological heterogeneity. The EAC agrees with the use of the overall value for the base case but has assessed the effect of the different ranges in scenarios.

Sequelae of CAUTI

The risk that CAUTI will progress to a blood stream infection (CABSI) is determined from Smith et al (2019). They used patient-level data to quantify the prevalence of CABSI defined as adult inpatients with urinary catheter-associated, urinary source infection. Hospital-onset infection was defined as patients with infection onset >48 h after admission and was reported as 4.8% (2524/52,085). However, this is hospital-acquired CABSI as a proportion of *all* inpatient CAUTI, including community-acquired (i.e. patients admitted with CAUTI, who then develop CABSI). This is therefore an underestimate of the number of patients who develop CABSI after starting their catheterization in hospital. Hospital-onset CABSI as a proportion of hospital-onset CAUTI is 6.6% (2,524/38,084). This is also not exactly what is wanted, which is the proportion of hospital-acquired CAUTI that develop into hospital-acquired CABSI. The numerator here includes patients admitted with community-acquired CAUTI who then develop hospital-onset CABSI. The denominator includes patients who are admitted with an indwelling catheter. However, this is the best estimate available from the published data. The EAC has therefore used a value of 6.6%, with a sensitivity range determined from the confidence intervals reported in Smith et al (2019): 5.0% to 9.8%. We could not do a similar calculation for community-onset CABSI as the total number of community-onset CAUTI is not reported in this study. CG139 referred to lower values for CABSI risk from a 2000 systematic review for inpatients with catheters up to 10 days (Saint et al 2000). In the absence of better estimates,

the EAC will also use 6.6% for community risk of CABSI. CABSI in-hospital mortality (19.5%) was estimated from patients with *E. coli* bacteraemia.

For community-based patients conducting ISC, CG139 estimated CABSI rates using a systematic review published in 2000 and based on patients in a hospital setting. This value is slightly smaller (3.6%), but as it is much older and not based on UK populations the EAC has not used it. The value for mortality from CABSI in CG139 is much smaller (7.7%) and is based on a 1991 single study of small numbers infection in patients conducting ISC who have spinal cord injury. The EAC agree that the values from Smith et al (2019) are the most appropriate available. The values for mortality are not used in the cost-consequence decision tree, but only used to determine the number needed to treat (NNT) with UroShield to avoid one death from CABSI.

In the community, consideration is made for antibiotic resistance and the proportion of infections that fail to respond to initial treatments. In CG139 the sensitivity analysis addresses a population of patients conducting ISC who do not have spinal cord injury (SCI), in order to make the results more generalisable. In this population, 8% of infections do not respond to first line treatment, and another 6% (of the initial population) have multi-drug resistant (MDR) infections. However, the EAC consider that these probabilities have not been correctly implemented in the model. CG139 indicates that 14% of non-SCI patients fail first line treatment, comprised of 8% that are resolved with second line antibiotics and 6% that have MDR. However, the 6% who have MDR have second line treatment first. Therefore 14% of patients with CAUTI have second line treatment in total, and 6% additionally have MDR treatment. In the submitted model only 8% have been allocated second line treatment costs. The EAC have changed this to 14%.

Duration of catheterizations.

Mean duration of catheterizations in hospital is estimated as 10 days by the company. This is based on the mean duration of 3 days in patients expected to need a catheter for no more than 14 days (Pickard et al. 2012). In this study

patients were primarily catheterized following elective surgery and the company suggest that non-elective surgery may result in longer durations. The EAC was not able to identify any recent UK data regarding duration of catheterizations in hospital. However, duration of catheterization is only used to determine UroShield costs so longer estimates are conservative and favour SOC.

Table 12: Clinical parameters used in the company's model and any changes made by the EAC

Parameter	Company submission	Source	EAC value	Source	Comment
Effectiveness of UroShield (RR)					
Base case	0.252	Meta-analysis	Same		Based on meta-analysis from clinical submission. Mix of long term (>28 days) and short term (≤28 days) users in the meta-analysis Pair-wise values checked in scenarios.
Risk of CAUTI without UroShield (hospital)					
Hospital - All	3.80%	Smith (2019)	Same		Appropriate source for hospital setting from recent UK study.
Hospital ≤28 days	3.45%	Smith (2019)	Same		Determined as halfway between the value for 2 days 3.1% and the mean overall value of 3.8%. Reasonable approach in the absence of better data and to represent the increase in risk with catheter duration.
Hospital >28 days	10.17%	Smith (2019)	Same		Determined as a linear interpolation between 3.1% at 2 days and 13.2% at 60 days. Reasonable approach in the absence of better data and to represent the increase in risk with catheter duration.
ICU	3.80%	Smith (2019)	Same		Same as the overall values.
Risk of CAUTI SOC (hospital)					
Community - All	8.50%	Getliffe & Newton (2006)	Same		Best available value from UK study.
Community - Recurrent	25.00%	Assumed 2 every three months	Same		Based on the EAU definition of UTI recurrence
CAUTI sequela					
Probability CAUTI in community fails first line antibiotics	8.00%	CG139, Appendix J, Table 29	14%	CG139, Appendix J, Table 29	8% is the proportion that *only* need 2nd line antibiotics, whereas the model requires that patients who have MDR also get 2nd line treatment. So this should be 8%+6%=14%.
Probability CAUTI in community is multi drug resistant	6.00%	CG139, Appendix J, Table 29	Same		Note that CG139, table 25 includes MDR mortality. This is not in the model, but will not affect costs.
Probability CAUTI develops into bacteraemia	4.80%	Smith (2019)	6.6%	Smith	Re-calculated hospital-acquired CABSI in hospital-acquired CAUTI. Recent UK study.
Death from bacteraemia	19.50%	Smith (2019)	Same		Appropriate source for hospital setting from recent UK study.
Average length of time catheterised in hospital					

Hospital - All	10	Assumption	Same		No other data on which to base estimates, only used for UroShield costs.
Hospital ≤28 days	7	Assumption	Same		No other data on which to base estimates, only used for UroShield costs.
Hospital >28 days	42	Assumption	Same		No other data on which to base estimates, only used for UroShield costs.
ICU	10	Assumption	Same		No other data on which to base estimates, only used for UroShield costs.

Resource identification, measurement and valuation

The costs and resources included in the model are reported in table 13. The costs of the technology are balanced again the costs per CAUTI avoided by the use of UroShield.

Hospital costs

Patients acquiring a CAUTI during a hospital stay will incur additional costs to treat the UTI on top of whatever treatment or procedure they were admitted for. The company have used a value of £1,968 reported in the EPIC3 guidelines (Loveday et al 2014) for these excess costs. This is based on a study that used NHS data from 1995 (Plowman et al 2001). It can be expected that procedures and standards of care have changed significantly since this time. However, no more recent UK data has been identified. The 2014 value has not been uprated by the company in order to be more conservative. (The higher the cost of treating a CAUTI, the greater the likely cost savings are for UroShield.) The HRG s for 'Kidney or urinary infections' (LA04H-LA04M) are identified by the company as the most appropriate Reference Costs to use as a comparison. The company report the weighted average of long-stay non-elective admissions as £2,852. This has subsequently been amended to £2,809. Short-stay admissions may have been excluded as these are for 2 days or less and it is generally considered that a catheter-induced infection takes around 2 days to develop (Bonkat et al 2021). Non-elective admissions massively outweigh elective admissions, which are less costly in general.

Smith et al (2019) and Kilonzo et al (2014) both report much lower hospital costs for treating UTIs of £532 and £573 respectively. These are both based on the study by Pickard et al (2014). In this study, costs were estimated in a top-down approach, separating overall costs of hospital, outpatient, and primary care for patients with 3 types of urinary catheter, and assessing the total differences between those with and without UTIs. The company argue that this cost is inappropriate as the patients in that study were undergoing elective procedures and appears to include outpatient and primary care costs incurred for infections up to 6 weeks after the hospital stay. Notably, the estimate given above from Smith et al (2019) does not include costs for

excess bed days, which are an additional cost (0.63 days per CAUTI). It is not clear how (or whether) Smith et al separated the LOS costs from the Pickard results.

These estimates are difficult to interpret and apply to the UroShield population. The company argue that the patients in the Pickard study are likely to be healthier than a typical CAUTI patient. As patients having non-elective procedures appear to dominate the Reference Costs, this appears to be reasonable. The company have not uprated the 2014 EPIC3 estimate in order to be more conservative and it is very similar to the Reference Cost estimate. The EAC accept the company's estimate for the base case, but have increased the range of values used in the sensitivity analysis.

For patients in ICU, the company used a meta-analysis that reported the excess LOS for patients in ICU with CAUTI (Chant et al 2011). The company chose to use the lower estimate from the fixed effects model as a conservative estimate. This was erroneously reported in the company submission and included in the model as 2.3 (2.0-2.6) days. The EAC has corrected this to 2.6 (2.3-3.0) days. No other treatment costs are included and the cost of a bed day in ICU (£1,218) is taken from 2018-19 Reference Costs. The calculation for this is a weighted average of the day cost for all critical care environments, including paediatric and neonatal. As all the other data used in the model is based on adult populations it makes sense to only include adult ICUs. For the 2018-19 Reference Costs used by the company this increases the daily rate to £1,428. The EAC have also updated this using the recently released 2019-20 Reference Cost data, which result in a daily ICU cost of £1,620. This method may underestimate the cost of CAUTI in ICU patients by not accounting for additional treatment requirements. However, this is again a conservative approach and the EAC accepts the values provided.

For the patients who develop CABSI the costs of treatment (£3,401) are taken from Smith et al (2019). Again, this does not include the costs of excess LOS for CABSI, which are given as 1.83 days and would be in addition to the CAUTI LOS.

The mean cost per CAUTI (including complications) are not reported separately in the model, but are derived from the cost per CAUTI per patient plus the cost of

CABSIs for the proportion of patients where they occur. For CAUTIs occurring in hospital, the company mean cost per CAUTI is £2,131, based on hospital treatment costs (£1,968) and the occurrence of CABSI in 4.8% of patients (at a cost of £3,401 each). For patients in ICU, the mean cost per CAUTI is £2,964, based on the excess bed days (2.3 x £1,218) and the same proportion of patients developing CABSI. In the EAC base case, these values are £2,192 (£1,968, plus 6.6% of £3,401) and £4,436 (2.6 x £1,620, plus 6.6% of £3,401) respectively.

Community costs

The cost of treating a CAUTI in the community is taken from CG139 and includes first line treatment for all, 2nd line treatment where initial antibiotics fail, 3rd line (hospital) treatment for multi-drug resistant (MDR) infections, plus treatment for CABSI. The company have uprated these costs for each of these states using the inflation rates in PSSRU (Curtis et al 2020). (It is not possible to recreate the CG139 costs with current prices as the precise components are not reported.) The cost of a catheter change (calculated) is added to the costs for 1st and 2nd line treatments. For example, the total amount for 1st line treatment given in CG139 is £32.20 and the company has inflated this to 2019 prices to give £43.25 plus £28.10 for a catheter change.

The average cost of treating community CAUTI is higher in the Excel model than the written submission: £386.72 versus £372.41. The EAC assumes this was a typographical error in the written submission as the results remain consistent. The company indicate that recurrent CAUTI may require higher levels of care (including hospital admissions), so this is conservative for this subpopulation. The rates for CABSI and mortality are taken from Smith et al (2019).

The cost for a catheter change is calculated as catheter cost plus 15 minutes of nurse time. The cost of the catheter includes additional items such as lubricating gel and dispensing fee. This is taken from CG139 and uprated to current values of £5.87. However, the company has since indicated that the catheters for use in ISC in CG139 are cheaper than those used in longer-term catheterization. The EAC additionally suggest that a dispensing fee is not appropriate if the catheter change is

being conducted by a nurse (and therefore presumably supplied by the nurse). The higher cost of longer-term catheters is probably balanced out by the removal of the dispensing fee from this estimate and therefore the EAC accepts £5.87 as an appropriate estimate of the catheter cost.

The patients in CG139 were estimated to carry out ISC 5 times per day and use 5 catheters per month on average. In such patients CG139 suggests that, due to more frequent urination and drinking during UTIs, an average of 12 additional catheters are required per infection. However, EAU guidelines (Bonkat et al 2021) and online nursing guides suggest that a single catheter change is appropriate in non-ISC populations using UroShield.

In the UroShield model a nurse changes the catheter. There is potential for double counting of nurse time as part of the treatment cost in CG139 includes time to see a healthcare professional. However, only 10% of patients are considered to consult a nurse. The EAC consider it reasonable that both a diagnostic consultation and a treatment visit to change the catheter are included in the costs.

The CG139 cost for patients who have MDR infections and those who develop CABSI includes admission to hospital.

The average cost of treating a CAUTI in the community, accounting for treatment failures and CABSI, is £387 in the company base case and £454 in the EAC base case.

Technology costs

The technology costs are given as the number of actuators (1 per 30-day duration) and the daily cost of the generator. The costs are provided by the company and are fixed at £349 for the generator and £50 per actuator. The number of actuators is determined by the duration of catheterization and rounded up to a whole number. In the hospital population, short-term catheters (≤28 days) require 1 actuator, and long-term catheters require 2 (average of 42 days). The community model time horizon is a month; therefore the model includes a single actuator. The EAC do not consider it likely that a generator will be in use every day. In hospital, highly-used devices such

as infusion pumps require time for cleaning and maintenance even if kept on the ward. In the community, the device will additionally need to be delivered to and collected from each patient. Only if given to patients with permanent or semi-permanent catheters could the generator be considered to be 'in use' every day. The EAC has amended this so that the generator is out of use for 20% of its 2-year lifespan. (However, it is possible that this may extend the useful lifespan of the device by around 20%, thus cancelling out the resultant increase in per day technology costs.) The EAC's sensitivity analysis varies the in-use time from 100% to 60%.

Table 13: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	Source	EAC value	Source	Comment
ICU bed day	£1,218	NHS Reference Costs 2018/2019	£1,620	NHS Reference Costs 2019/2020	Weighted average cost for adult critical care
Excess ICU bed days	2.3	Chant 2011	2.6	Chant 2011	Correction from Chant 2011 (lower value of 2.3, upper value of 3). This would increase cost saving.
CAUTI Costs					
Community CAUTI (first line antibiotics excluding catheters)	£43.25	CG139	Same		CG139 costs based on NHS reference costs and BNF costs, and inflated to 2019/20
Community CAUTI (second line antibiotics)	£65.23	CG139	Same		CG139 costs based on NHS reference costs and BNF costs, and inflated to 2019/20
Community CAUTI (multidrug resistant)	£2,410.50	CG139	Same		CG139 costs based on NHS reference costs and BNF costs, and inflated to 2019/20
Community treated CAUTI	£386.72 (£372.41 in written submission)	Calculated	£453.54		Based on: **1st line** antibiotics + catheter change for all PLUS **2nd line** antibiotics + catheter change if 1st line fails (14%) PLUS

					MDR treatment (6.0%) PLUS **CABSI** cost for 6.6%
Excess cost of hospital acquired CAUTI	£1,968	EPIC3	Same		Conservative estimate of inpatient costs.
Excess cost of CAUTI CABSI	£3,401	Smith (2019)	Same		Direct hospital costs only, not including LOS.
Catheter change in Community					
Catheter	£5.87	BNF	Same		Not from BNF, from NHS drug tariff
Nurse Time	15 minutes	Assumption	Same		
Cost of Nurse time	£89	PSSRU 2020	Same		Based on one hour of patient contact time. Cost is £22.25 for 15 minutes (£89/4).
Total cost of catheter change	£28.10		Same		Cost of catheter plus 15 minutes of nurse time. Applied at 1st and 2nd line treatments.
UroShield costs					
Unit cost	£349	Company	Same		
Actuator cost	£50	Company	Same		
Unit lifespan (years)	2	Company	Same		
Actuator lifespan (days)	30	Company	Same		One actuator is used per patient in all settings except hospital settings >28 days where 2 are required.
Proportion of time in use	NA		80%	EAC	Accounts for generator not in use every day.
Cost of device per day	£0.48	Company Assumes in use 760 days over 2 years.	£0.60		Cost per day, assuming that it is in use 584 days over 2 years.

Sensitivity analysis

The Company submitted one-way sensitivity analysis in the form of tornado diagrams. The parameters that were varied are shown in table 14. The ranges were taken from the source or were ±25% of the base value.

Table 14: Sensitivity ranges used by the company

Parameter	Sub-population	Base	Low	High	Source
Risk ratio	All	0.252	0.112	0.566	Meta-analysis
Risk of CAUTI (SOC) (%)	All hospital	3.80	3.00	4.70	Smith (2019), ± 95% CI
	Hospital ≤28 days	3.45	2.59	4.31	Smith (2019); ± 25%
	Hospital >28 days	10.17	7.63	12.71	Smith (2019); ± 25%
	ICU	3.80	3.00	4.70	Smith (2019); same as overall
	Community	8.5	8.5	10	Getliffe & Newton (2006)
	Community recurrent	25	25	33	EAU definition
Duration of catheterisation (days)	All hospital	10	7.5	12.5	Company assumption
	Hospital ≤28 days	7	5.25	8.75	Company assumption
	Hospital >28 days	42	31.5	52.5	Company assumption
	ICU	10	7.5	12.5	Company assumption
Risk of 1st line AB failure (%)	Community	8	6	10	CG139
Risk of MDR (%)	Community	6	4	8	CG139
Risk of CABSI (%)	All	4.8	4.1	6.3	Smith (2019)
Excess cost of CAUTI	Hospital (not ICU)	£1,968	£1,476	£2,460	EPIC3
Additional bed days for CAUTI	ICU	2.3	2.0	2.6	Chant (2011)
Excess cost of CABSI	All	£3,401	£2,061	£5,613	Smith (2019)
Nurse time to change catheter (mins)	Community	15	10	20	Company assumption

The EAC altered the company's sensitivity ranges and added a parameter to account for the out-of-use time for the generator. These ranges are shown in Table 15.

Table 15: Sensitivity ranges used by the EAC

Parameter	Sub-popn	Base	Low	High	Source
Risk of CAUTI (SOC) (%)	Community	8.5	5	30	Getliffe & Newton (2006)
Risk of 1st line AB failure (%)	Community	14	10.5	17.5	CG139
Risk of CABSI (%)	All	6.6	5.0	9.8	Smith (2019)
Additional bed days for CAUTI	ICU	2.6	2.3	3.0	Chant (2011)
Generator in-use proportion	All	0.8	0.6	1.0	EAC assumption

The EAC also conducted a two-way sensitivity analysis for the risk of CAUTI and the effectiveness of UroShield in all six populations. The ranges for this approximated those used in the one-way analysis, adjusted to provide regular spacing of data points, but also including the specific values for the base case.

9.3 Results from the economic modelling

Base case results

The company and EAC base case results are shown in table 16. All of the scenarios presented are cost saving, except for general community use, which is around £40 cost incurring per month. The low cost of treating a community based CAUTI (£453.54) combined with the relatively low base rate of infection (8.5%), means that insufficient CAUTIs are saved in this scenario to balance the additional cost of UroShield. For the community patients with recurrent UTI, the cost of CAUTI is the same, however the base rate of infection is much higher (25%) resulting in an overall cost saving per month.

For hospital settings, the cost savings in the overall and short-term populations are rather marginal; around £6 overall and £2 in the short-term catheterization group.

The higher CAUTI rate for patients with long-term catheterization and the higher costs for ICU patients leads to higher cost savings in these groups.

In general, the combined changes made by the EAC to the base case have had little effect on the overall savings. The combined increase in bed days and daily costs for ICU patients in the EAC model mean that this is where the largest change from the company model occurs; from £30 to £70 cost saving per patient. Cost savings have also increased slightly in recurrent community infections.

Table 16: Summary of base case results

	Company Submission			EAC Results		
	SoC	**UroShield**	**Cost saving per person**	**SoC**	**UroShield**	**Cost saving per person**
Hospital - all						
Cost of CAUTI	£80.99	£20.41	£60.58	£83.31	£21.00	£62.31
Other costs	£0	£54.78	-£54.78	£0	£55.98	-£55.98
Total cost	£80.99	£75.19	**£5.80**	£83.31	£76.97	**£6.34**
Hospital ≤28 days						
Cost of CAUTI	£73.53	£18.53	£55.00	£75.64	£19.06	£56.58
Other costs	£0	£53.35	-£53.35	£0	£54.18	-£54.18
Total cost	£73.53	£71.88	**£1.65**	£75.64	£73.24	**£2.40**
Hospital >28 days						
Cost of CAUTI	£216.75	£54.62	£162.13	£222.97	£56.19	£166.78
Other costs	£0	£120.08	-£120.08	£0	£125.10	-£125.10
Total cost	£216.75	£174.70	**£42.05**	£222.97	£181.29	**£41.69**
Hospital – ICU						
Cost of CAUTI	£112.66	£28.39	£84.27	£168.59	£42.48	£126.10
Other costs	£0	£54.78	-£54.78	£0	£55.98	-£55.98
Total cost	£112.66	£83.17	**£29.49**	£168.59	£98.46	**£70.13**
Community – all						
Cost of CAUTI	£32.87	£8.28	£24.59	£38.55	£9.71	£28.84
Other costs	£0	£64.54	-£64.54	£0	£68.18	-£68.18
Total cost	£32.87	£72.83	**-£39.95**	£38.55	£77.89	**-£39.34**

Community – recurrent						
Cost of CAUTI	£96.68	£24.36	£72.32	£113.38	£28.57	£84.81
Other costs	£0	£64.54	-£64.54	£0	£68.18	-£68.18
Total cost	£96.68	£88.90	**£7.77**	£113.38	£96.75	**£16.63**

Sensitivity analysis results

The company's Tornado results indicate that the effectiveness of UroShield has the single greatest effect on cost-savings in all models. See Appendix D for The Tornado diagrams for the one-way sensitivity analysis and data table for the two-way sensitivity analysis.

Hospital settings

For hospital populations, the following had the largest effects on cost savings in the company's model:

- Effectiveness of UroShield (relative risk)
- CAUTI rates (SOC)
- Cost of treating CAUTI (treatment costs or ICU bed days)

The EAC changes did not change these top three parameters, only the rankings; reflecting the wide sensitivity ranges used, the excess cost of treating CAUTI had the largest influence in the EAC model, except for in the ICU setting. The risk and cost of treating CABSI had minor effects on the cost outcome in all hospital settings. The proportion of time that a generator was in use was of negligible influence, as was duration of catheterization except in the long-term population. The actuator costs have substantial influence at certain points in long term catheter durations. Due to the £50 step change in the technology costs every 30 days, increasing the catheter duration from 58 days to 62 days (for example) reduces the cost saving in the long stay population from £76 to £35.

Where base case cost savings were small (overall hospital and short-term populations), any one of the top three parameters could convert the base case from cost-saving to cost-incurring. Where cost savings were larger (ICU and long-term), only effectiveness of UroShield could independently convert the base case to cost-

incurring in the company model. In the EAC model, the ICU setting remained cost saving to all one-way changes, but both cost of CAUTI treatment and effectiveness of UroShield could affect this in long term populations.

The main sources of uncertainty in the hospital setting are the effectiveness of UroShield, cost of treating CAUTI, and the rate of CAUTI. From the meta-analysis, UroShield reduces infection by between 45% and 90% (95% CI). In the EAC sensitivity analysis the cost of treating CAUTI in hospital was varied from £530 to £2,460, reflecting the range of published values available. The rate of CAUTI in hospitals taken from Smith et al (2019) has a wide 95% confidence equivalent to around 21-24%. This is due to the methodology which used a point-prevalence survey across 9 NHS Trusts to estimate prevalence across all NHS Trusts.

It is notable that, despite high costs and wide sensitivity ranges, CABSI has very little influence on the cost outcomes in hospital settings.

Scenarios were included to look at the effect of using the meta-analysis pair-wise estimates for the effectiveness of UroShield. The effectiveness is lower in the short-term (0.318) and greater in the long term (0.230) populations. As a result, in patients with short term catheter durations the base case goes from £2.40 cost-saving to £2.60 cost-incurring, and the hospital long-term base case increases from £41.69 cost saving to £46.59 cost saving

Community setting

Alongside risk of CAUTI and effectiveness of UroShield, the risk and cost of treating CABSI are significant influences on cost outcomes in community-based patients. This is due to the high treatment costs of this condition relative to those for CAUTI in this setting.

For the cost-incurring, overall community population, only risk of CAUTI can independently convert the base case to cost-saving. Changes to the base case (approximately £39 cost-incurring) are generally quite small (±£10 or less). For rates of CAUTI greater than about 25% UroShield becomes cost saving. According to Getliffe and Newton (2006), these rates may occur in nursing homes. The low cost of

treatment means that UroShield is not cost-saving under any other one way sensitivity variations.

For the recurrent community population, the risk of CAUTI is only increased in the sensitivity analysis as the company used the minimum frequency of infections in their base case. Effectiveness of UroShield is the only parameter that can independently change the outcome from cost saving to cost incurring (although using the minimum cost of treating CABSI reduces the cost saving from £16.63 to £0.10).

Two-way sensitivity analysis

The cost outcomes when the UroShield effectiveness ratio and risk of CAUTI are varied together are shown in Appendix D. As the risk of CAUTI increases, UroShield is more likely to be cost-saving. Alternatively, as the effectiveness increases, UroShield is cost-saving in more populations.

In the ICU setting, virtually all combinations of effectiveness and infection risk remain cost-saving. In the overall community setting, even if UroShield reduced CAUTI by 80-90% it would only be cost saving in populations where the rate of CAUTI was greater than 15-20%. In the community recurrent population, the lower value for CAUTI rate has been extended down so that the definition of 'recurrent' infection starts at 1.8 per year (15% monthly risk), rather than 3 (as per the EAU definition, and 25% monthly risk). In the one-way sensitivity analysis, this parameter was only varied upwards from the minimum value in the EAU definition.

The table in Appendix D further demonstrates how the base case value fits into the sensitivity ranges and how the change between cost-saving and cost-incurring is affected by the variations in these two parameters.

Additional results

The company additionally conducted an analysis to determine the number of patients needed to treat (NNT) with UroShield in order to avoid one death. In the company's model this varied from 571 in the recurrent community population to 4,140 in the

short-term hospital population (Table 17). In the EAC model, this is reduced to 416 in the recurrent community and 3,011 in the short-term hospital populations.

Table 17: NNT to avoid one death from CABSI

NNT	Company Model	EAC model
Hospital - All	3759	2734
Hospital ≤28 days	4140	3011
Hospital >28 days	1404	1021
ICU	3759	2734
Community - All	1680	1222
Community - Recurrent	571	416

9.4 The EAC's interpretation of the economic evidence

The EAC has accepted the overall model structure and most of the input parameters for the company's economic model. We have redrawn the model structure so that it is more consistent with the data used in the model, but this does not affect the calculations or results. The EAC has corrected or altered several of the input parameters. However, the combined effect on the cost outcomes is generally small and does not affect whether the base case is cost-saving or cost-incurring in any population. The increase in cost savings in the ICU setting and recurrent community population are the largest changes in the base case results.

The populations included in the models match the overall population in the decision problem (people with indwelling urinary catheters across hospital and community settings) and one of the specified subgroups (recurrent infections, only in the community). There was no reference to catheter duration in the Decision Problem populations. However, as CAUTI risk increases with catheter duration, the separation of short and long-term subpopulations in the model could be seen as addressing lower and higher risk groups. ICU was identified as a setting in which patients are more likely to be given prophylactic antibiotics. The use of UroShield in these patients may affect hospital prescribing strategies and assist in limiting antibiotic resistance. Notably, the economic case is strongest in the higher risk

subpopulations (long-term and recurrent infections) and in the highest cost setting (ICU).

The main issues for acceptance of the economic case presented are:

- the use of bacteriuria in the studies as a proxy for CAUTIs averted by UroShield,
- the uncertainty in the effectiveness of UroShield at preventing CAUTIs, and whether this varies across settings and subpopulations,
- the uncertainties in the rate of CAUTI,
- the uncertainties in the costs of treating CAUTI in hospital.

The significant uncertainties in several of the input values means that we cannot draw conclusions about the exact values of the cost outcomes. In subpopulations where savings are marginal, UroShield may easily end up cost-incurring. Despite this, the sensitivity analysis shows that UroShield is extremely likely to be cost saving in an ICU setting and very likely to be cost-saving in community-based patients who have 3 or more CAUTIs per year.

10 Conclusions

10.1 Conclusions from the clinical evidence

The clinical evidence is currently very limited both in quality and quantity, although all studies are relevant to the decision problem and meet the PICO elements of the scope. Studies vary in how UroShield is used with some studies comparing with a sham device, some comparing with standard care without UroShield and some looking at changes from baseline in the same patients. There is limited evidence from 3 studies that UroShield can reduce in bacteriuria and infections in people with long-term catheters (Markowitz 2018, da Silva 2021, Nagy 2011). The evidence for the benefit of UroShield in patients with short-terms catheters is very limited and does not suggest any clinical benefit at this time. No other subgroup analysis or risk group analysis is available.

Overall, the EAC consider that the UroShield device is safe and easy for patients and shows promise for the prevention of CAUTIs. There is currently not enough good quality evidence to support routine adoption of the UroShield device however the EAC consider that further research within an NHS setting would be beneficial.

10.2 Conclusions from the economic evidence

The economic findings are driven by the base rate of CAUTIs in the specified population, the reduction in these due to the use of UroShield, and the cost of treating CAUTI. The higher the risk of CAUTI and the cost of treating it, the more likely UroShield is to be cost-saving. Where treatment costs are low, as in the general community population, UroShield is cost incurring. This is a population in which the company and clinical experts expected UroShield to be of greatest utility. For some community patients with a higher risk of UTI (patients having recurrent UTIs) UroShield can result in cost savings, even with the lower cost of treatment.

Where the cost per CAUTI is higher (hospital population), all the submitted subpopulation resulted in cost savings. These are greatest where there is a

longer period of catheterization (and therefore higher number of CAUTIs), or where the cost per CAUTI is higher, as in ITU population. However, these outcomes are based on the effectiveness of UroShield taken from poor quality studies that measured asymptomatic bacteriuria rather than symptomatic CAUTIs.

11 Summary of the combined clinical and economic sections

The clinical evidence is currently very limited both in quality and quantity, although all studies are relevant to the decision problem and meet the PICO elements of the scope.

Although the UroShield device is safe and easy for patients and shows promise for the prevention of CAUTIs, there is not enough evidence to support routine adoption at this time. Patients who use the device report positive outcomes both clinical and quality of life related. It is cost-saving in populations with higher rates of CAUTI and/or higher treatment costs. However, the economic case is based on an assumption that bacteriuria is an appropriate proxy for CAUTIs requiring treatment and on effectiveness results with high uncertainty.

The EAC conclusion is that more research is needed to confirm the early positive results shown for people with long-term catheters and to determine whether people with short-term catheters would benefit from using UroShield particularly if they are considered high risk of infection.

12 Implications for research

The company submission included a number of claimed benefits of the UroShield device and some of these claimed benefits have been met or partially met by the current evidence. The EAC considers that the UroShield device shows promise, however there are still gaps in the evidence (table 18).

Table 18: Summary of Claimed Benefits

Claimed Benefits	Supporting Evidence	Rationale	EAC Comment
Patient benefits			
Preventing catheter associated urinary tract infection (CAUTI), potentially leading to a reduction in the incidence of CAUTI.	Markowitz et al, 2018; Zillich et al, 2014; Nagy et al, 2011; Ikinger et al, 2007; Da Silva 2021; Shenfeld and Haris, 2010.	All studies showed either a reduction in bacteria/CFU or bacteriuria which in turn results in a reduction in UTI and CAUTI.	***Partially met*** The EAC agree that the current evidence suggests that use of UroShield reduces bacterial load and infections in patients with long-term catheters however the evidence for short-term catheterisation is less conclusive. Further research to confirm the early, promising results would be beneficial.
Improved quality of life in people with indwelling urinary catheters with minimal disruption to patients' daily activities	Da Silva 2021; Zalut (2017)	Da Silva included qualitative feedback and analysis which indicated that overall patient wellbeing was improved with UroShield. Zalut (2017) reported an overall increase in wellbeing score from 3.3 to 7 over 4 days with UroShield	***Met*** The EAC agree that the Da Silva study indicated that patient well-being was improved with UroShield however this was a small study. While Zalut et al (2017) reported an increase in wellbeing score, details of how this was assessed are limited due to this being a poster. Further quality of life studies with a larger number of patients would be beneficial.
Reducing catheter-related pain, spasm and discomfort.	Nagy et al, 2011; Zalut 2017; Da Silva 2021; Shenfeld and Haris, 2010	All studies reported a reduction in pain, spasm and discomfort scores.	***Met*** The EAC agree with the evidence that use of UroShield is associated with reduction in pain, spasms and discomfort in users. However, all studies are small with limited reporting of methods.
System benefits			
Reducing the use of antibiotic prophylaxis	Zillich et al 2014	Zillich demonstrated improved outcomes for patients with just UroShield compared to control group treated with additional antibiotics (trimethoprim).	***Not Met*** The study was not designed to assess whether antibiotic use was reduced with UroShield.
Ease of implementation; minimal changes in facilities or infrastructure	Da Silva 2021; Shenfeld and Haris, 2010; Zalut 2007	User feedback on ease of use and overall tolerability. Zalut reported that UroShield could be	***Met*** UroShield is easy to use, requires minimal training and does not require any change to current pathway for catheter

needed if UroShield adopted in standard practice		used in the home care setting.	management as it is an additional prophylactic option. It can be used in both hospital and community settings and can be easily managed by the patient. User feedback is largely positive however it should be noted that there were some negative comments relating to comfort of the device at night and battery life.
Cost benefits			
Reduction in costs and resources that could be associated with treating CAUTI such as additional clinician visits, hospital admissions and the use of antibiotics	Shenfeld and Haris, 2010 Da Silva 2021	Shenfeld and Haris reported that the overall pain medication use was reduced in the UroShield group. Da Silva reported a significant reduction in antibiotic use over 12 weeks in NHS patients.	***Unclear*** Both clinical and economic evidence for a reduction in costs and resources is extremely limited. While DaSilva (2021) does report a reduction in antibiotic use over 12 weeks, The cost of antibiotic treatment is low. Economic analysis indicates that where treatment costs are low, as in the general community population, UroShield is cost incurring. For subgroups where infections rates are higher (such as recurrent infection) UroShield can result in cost savings, even with the lost cost of treatment. For a hospital population with higher treatment costs, the model showed a greater likelihood of UroShield being cost saving.
Reduction in health service resource use that could be associated with the use of catheter such as avoiding catheter blockages, a reduction in the frequency of catheter changes and bladder washouts.	Da Silva 2021	Da Silva reported a significant reduction in catheter changes but not bladder washouts over 12 weeks in NHS patients	***Not Met*** The clinical evidence that UroShield reduces the number of catheter blockages, frequency of changes and bladder washouts is limited to one study (DaSilva) which is a small study and specific to long-term catheters. It is currently unclear whether this limited clinical evidence translates into cost benefits and this was not included in the submitted cost model More research, with larger studies is needed to fully understand whether a) UroShield reduces blockages and b) frequency of catheter changes and the impact these have on cost savings.
Sustainability benefits			
Reduced number of catheters due to increased length of time between changes	Da Silva, 2021	Number of catheter changes reduced from a baseline value of 2.91 to 0.32 (p=0.001) after 12 weeks of UroShield use.	***Not Met*** The clinical evidence that UroShield reduces the number of catheter blockages, frequency of changes and bladder washouts is limited to one study (DaSilva) which is a small study and specific to long-term catheters.

			More research, with larger studies is needed to fully understand whether UroShield reduces blockages and frequency of catheter changes.

The EAC consider that additional research is needed to support the early promising results reported in the currently available literature.

The EAC has identified some key considerations for decision makers when considering research approaches

- The current research points towards a possible benefit for people with long-term indwelling catheters however larger studies are needed to determine whether the benefits observed in the small studies currently available can be validated. Consideration needs to be given as to what counts as a ‘good outcome’ for patients and the EAC suggests that a well conducted ‘before and after’ evaluation might be the best approach.

- There is estimated to be a high number of people with indwelling catheters who are at risk of CAUTI and therefore there may be an unmet need to be addressed. However, there is a lack of data around the number of people with long-term indwelling catheters and the rates of infections, without which it will be difficult to assess the impact of UroShield in the NHS as a whole. Currently, the evidence points towards a reduction in infections with UroShield. However, if the base rate of infections in a hospital or community setting such a nursing home is already low, then the impact of UroShield will be minimal.

- Antibiotic resistance was identified by clinical experts as a potential problem in this patient group and prophylactic use of antibiotics is not routinely recommended. As a prophylactic device, UroShield may have a place as an alternative to antibiotics and, if the use of UroShield does reduce infections, may reduce the need for therapeutic antibiotics. However, this needs to be investigated.

- Consideration is needed as to whether bacteriuria or significant bacteriuria is a suitable proxy measure for infection. The company state that UroShield should not be used during active infection, however significant bacteriuria may be indicative of asymptomatic infection. Definitions of 'infection' are notoriously vague and variable across conditions. The outcome of interest is CAUTI in need of treatment, however treatment thresholds are also likely to be variable between settings and sites.

- Patients with long-term indwelling catheters and recurrent infections are likely to have poor quality of life outcomes. Consideration should be given to assessing whether UroShield, in addition to current management and care, can improve quality of life outcomes in this patient group.

- Patient level costing has been implemented in England and Wales for several years. Hospital costs of CAUTI treatment could be identified much more accurately if access to these datasets could be achieved.

- Any additional research should account for variations in practice, in catheter use, catheter care, and treatment protocols, both between sites and over time.

13 References

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14 Appendices

Appendix A: Decision Problem

Appendix B: Clinical and Economic Evidence Identification

Appendix C: Risk of Bias Assessment

Appendix D: Sensitivity Analysis

Appendix A: Decision Problem

	Scope
Population	People with indwelling urinary catheters across hospital and community settings.
Intervention	UroShield in addition to standard care
Comparator(s)	Standard care for preventing catheter associated urinary tract infection, including clinical observation such as documenting catheter blockages, reviewing the frequency of planned catheter changes, increasing fluid intake, and using prophylactic antibiotics when needed.
Outcomes	The outcome measures to consider include: • Incident rate of catheter associated urinary tract infection (CAUTI) • Rate of recurrence of CAUTI • Bacterial count in urine samples • Bacterial colonization levels (i.e. colony forming units) • Biofilm formation on the catheter lumen • Number of catheter changes • Number of catheter blockage • Antibiotics use • Number of outpatient visits • Number of hospital admissions including emergency admission to hospital • Reported pain and spasm • Ease of use (for patients and healthcare professionals) • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the different treatment options being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.

Subgroups	• People at high risk of developing CAUTI (for example, those with co-morbidities including diabetes or underlying neurological conditions; those in clinical settings such critical care units). • People who have recurrent episodes of urinary tract infection (for example, 2 or more episodes in a 6-month period).	
Special considerations, including those related to equality	In adults, women are more likely to develop a catheter-associated urinary tract infection than men. Cerebrovascular disease and paraplegia are associated with an increasing likelihood of catheter-associated urinary tract infection. Sex and disability are protected characteristics under the Equality Act. Urinary tract infection is an important cause of morbidity and antibiotic use in older adults. Age is a protected characteristic under the Equality Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No

Appendix B: Clinical and economic evidence identification

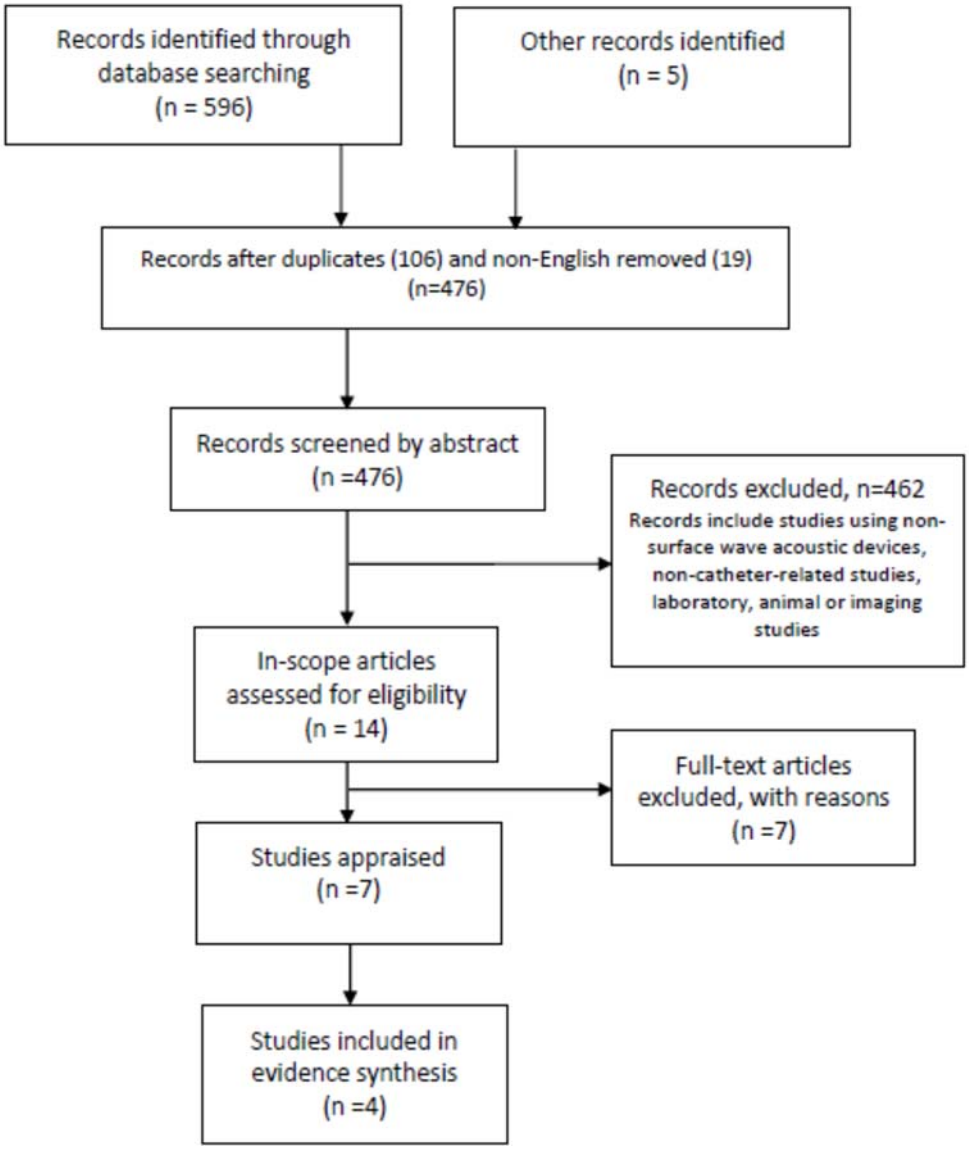
Company search strategy, screening criteria and process for clinical and economic evidence

A literature search, encompassing the key components of the decision problem, was performed in 4 databases (Medline, PubMed; Embase and CINAHL using the HDAS platform) to include the period from 2000 to 17th May 2021. A search of the company website and 2 grey literature databases was also performed to identify additional relevant studies. The search strategies were comprehensive using a combination of free text terms and indexed terms, it was noted that the terms used to describe the device were broad rather than specific and did not include incorporate truncation i.e. 'surface acoustic waves' not 'surface acoustic wave*' which would fail to identify records that contained 'Surface Acoustic Wave Actuator'. The company also limited the searches to English language publications and those described as

a clinical or controlled trial. The company searched 4 clinical trial registry platforms for ongoing studies.

No studies relevant to the economic submission were identified.

Company study selection for clinical evidence



Company search strategy for adverse events

The company conducted a search for adverse events in the MHRA, FDA MAUDE and Therapeutic Goods Administration regulatory databases. No records associated with UroShield were identified.

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched to include the period from database inception to 27th May 2021, using a range of free text terms and, where appropriate, indexed terms, the searches were not restricted by language of publication. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the FDA MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
27/05/21	Cochrane Library CDSR CENTRAL	 0 7	
27/05/21	CRD (DARE, NHS EED)	0	
26/05/21	EMBASE	12	
26/05/21	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	6	
14/05/21	PubMed	0	
27/05/21	Scopus	8	
27/05/21	Web of Science	6	

22/04/21	company website: https://www.sedanamedical.com/	9	
			Total records from databases: 21
29/04/21	FDA MAUDE adverse events	0	
29/04/21	MHRA – search MDA & FSN	0	
29/04/21	Clinicaltrials.gov	3	**Total clinical trial records: 6** (deduplicated against published results retrieved from database searches)
05/05/21	EU-CTR	0	

EAC Search strategies

The Cochrane Library

ID Search Hits

#1 MeSH descriptor: [Catheters, Indwelling] this term only 1032

#2 MeSH descriptor: [Urinary Catheters] this term only 93

#3 ((urinary NEAR/3 catheter*)):ti,ab,kw (Word variations have been searched) 1920

#4 ((Indwelling NEAR/3 catheter*)):ti,ab,kw (Word variations have been searched) 2124

#5 #1 OR #2 OR #3 OR #4 3574

#6 MeSH descriptor: [Ultrasonic Waves] this term only 23

#7 ((uroshield)):ti,ab,kw (Word variations have been searched) 5

#8 (ultrasound NEAR/3 prevent*):ti,ab,kw (Word variations have been searched) 56

#9 (acoustic NEAR/3 prevent*):ti,ab,kw (Word variations have been searched) 6

#10 ("surface acoustic waves"):ti,ab,kw (Word variations have been searched) 7

#11 ("surface acoustic wave*"):ti,ab,kw (Word variations have been searched) 7

#12 ("acoustic energy"):ti,ab,kw (Word variations have been searched) 17

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 109

#14 #5 AND #13 7

CRD

Zero results for: (uroshield) IN DARE, NHSEED

Zero results for: (ultrasound prevent) OR (acoustic prevent) OR (Surface Acoustic Wave) IN DARE, NHSEED

EMBASE <1947-Present>

1 exp indwelling catheter/ 18315

2 (urinary adj3 catheter*).tw. 10752

3 (Indwelling adj3 catheter*).tw. 13444

4 or/1-3 33493

5 "acoustic energy".tw. 1185

6 uroshield.tw. 3

7 ((Ultrasound or acoustic) adj3 prevent*).tw. 433

8 "surface acoustic wave*".tw. 1252

9 or/5-8 2853

10 4 and 9 12

INAHTA

((indwelling catheter) OR (urinary catheter)) AND ((uroshield) OR (ultrasound prevent) OR (acoustic prevent) OR (Surface Acoustic Wave)) FROM 1980 TO 2021: 0 records

---

Ovid MEDLINE(R) ALL <1946 to May 24, 2021>

1 catheters, indwelling/ or urinary catheters/ 19744

2 (urinary adj3 catheter*).tw. 6761

3 (Indwelling adj3 catheter*).tw. 8584

4 or/1-3 30323

5 Ultrasonic Waves/ 2452

6 uroshield.tw. 0

7 ((Ultrasound or acoustic) adj3 prevent*).tw. 309

8 “surface acoustic wave*”.tw. 1773

9 “acoustic energy”.tw. 939

10 or/5-8 4517

11 4 and 10 6

PubMed

Uroshield = 0

Scopus

TITLE-ABS-KEY (“indwelling catheter*” OR “urinary catheter*”) AND TITLE-ABS-KEY (“ultrasonic waves” OR “uroshield” OR “ultrasound prevent*” OR “acoustic prevent*” OR “surface acoustic wave*” OR “acoustic energy”) Result = 8

Web of Science

TS = ((uroshield) OR (ultrasound NEAR/3 prevent*) OR (acoustic NEAR/3 prevent*) OR ("surface acoustic wave*") OR ("acoustic energy")) AND TS = (indwelling NEAR/3 catheter*) OR TS = (urinary NEAR/3 catheter*) Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=All years
Result = 6

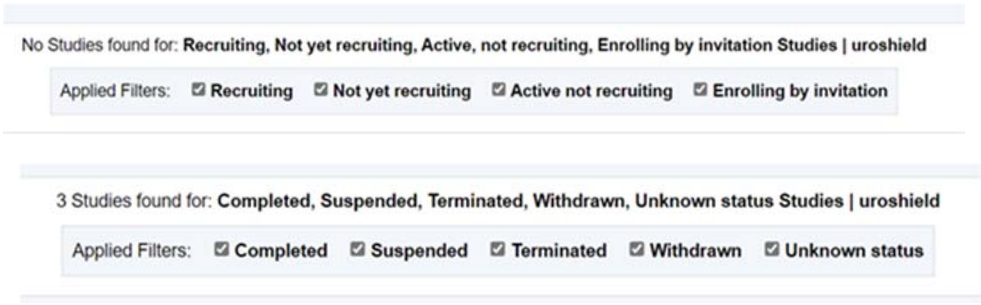
MAUDE

Searched for: Uroshield or Nanovibronix, Result = 0

MHRA

Searched for: Uroshield or Nanovibronix, Result = 0

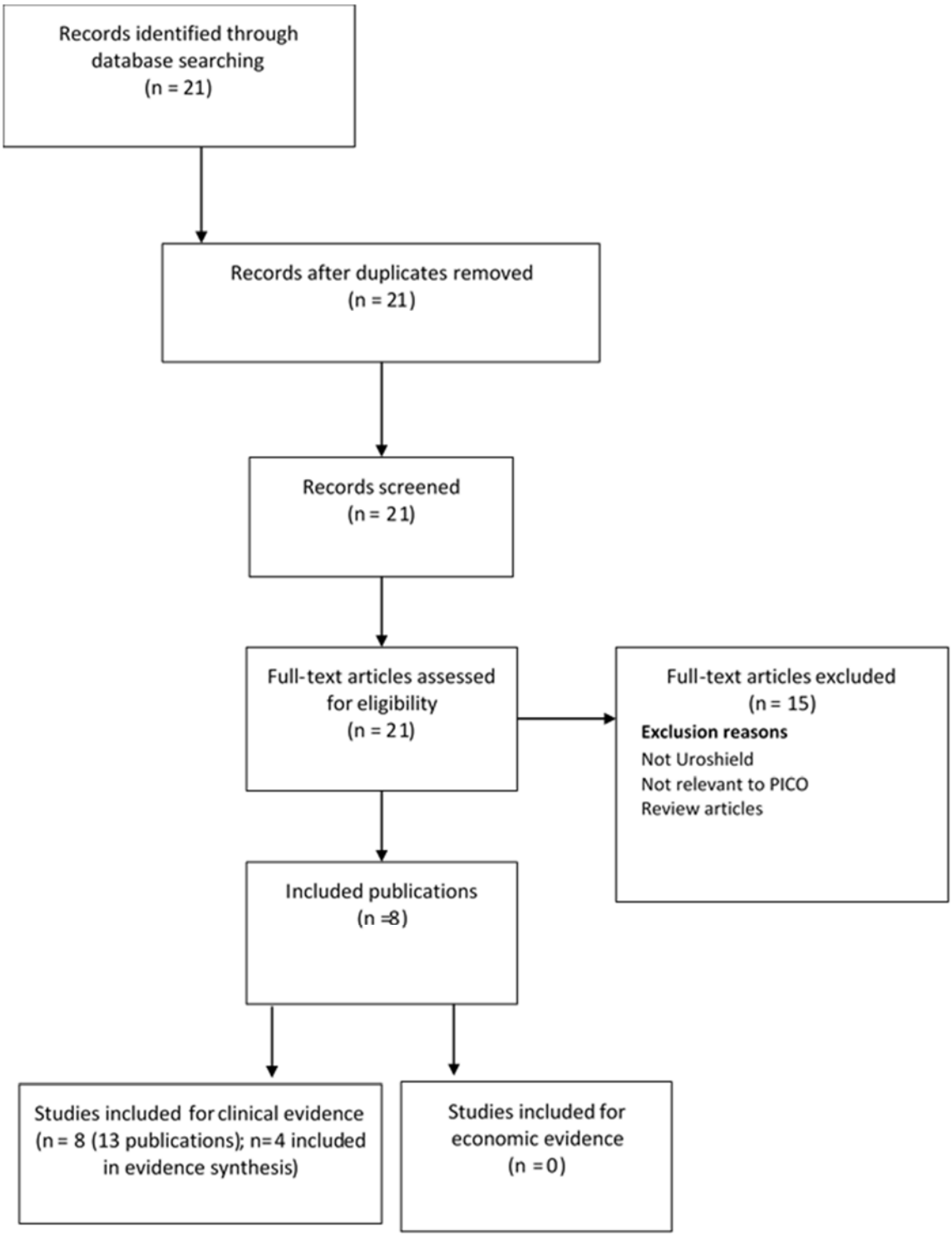
Clinical Trials.gov



EU-CTR

Searched for: Uroshield, Results = 0

EAC study selection



Appendix C – Risk of Bias assessment for Markowitz et al. (2018)

Study details

Reference	Markowitz S, Rosenblum J, Goldstein M, et a. (2018) The effect of surface waves on bacterial load and preventing catheter-associated urinary tract infections (CAUTI) in long-term indwelling catheters, *Medical & Surgical Urology,* 7(4), p. 210. ClinicalTrials.gov identifier: NCT03090373

Study design

X Individually-randomised parallel-group trial

☐ Cluster-randomised parallel-group trial

☐ Individually randomised cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	UroShield	Comparator:	sham device

Specify which outcome is being assessed for risk of bias	Bacterial colonisation: change in number of Colony-Forming Units (CFUs) between baseline and 30 days
Specify the numerical result being assessed.	Mean improvement advantage in treatment vs control = 87.2k CFU (t (53) 18.1, p<0.001)

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

✓ Journal article(s) with results of the trial

✓ Trial protocol

☐ Statistical analysis plan (SAP)

✓ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

✓ Conference abstract(s) about the trial

✓ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Journal article: "Subjects were randomized to either a control group or an active treatment group". See 2.1 & 2.2 – patients and investigators were blinded to treatment allocation.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Very little detail available about baseline differences between groups. Ambiguously reported in clinical study report (nothing in peer reviewed paper).	NI

Risk-of-bias judgement	Without baseline data it is not possible to know whether randomisation successfully divided the two groups equally. So one group may have had more risk factors than the other.	Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?	Without data there is no way of knowing what direction any effect might have taken.	Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Journal article: "Both subjects and the investigators were blinded as to which group the subjects were assigned to". There is no indication that blinding was unsuccessful, or that any unblinding was needed.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Journal article: "At baseline the CFUs for all groups both in the catheter and the urine assessment were 100k or greater. *There was thus no variability between or within groups*."	PN

2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		N
Risk-of-bias judgement	Blinding appears to have been adequate. Without baseline data it is not possible to know whether randomisation successfully divided the two groups equally. So one group may have had more risk factors than the other.	Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?	Without data there is no way of knowing what direction any effect might have taken.	Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Journal article: "Both subjects and the investigators were blinded as to which group the subjects were assigned to". There is no indication that blinding was unsuccessful, or that any unblinding was needed. The authors claim that UroShield vibrations are "barely felt" – but if they were detected, this could reveal that the patient is in the intervention group.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PN
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA

2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	There were no reported failures in implementing the intervention. However there is a statement which implies that treatment groups may not have been evenly distributed between sites. “because the study was conducted in a single network of Skilled Nursing Facilities, with a unified treatment protocol, the catheter care provided was similar, eliminating built-in bias because of differential treatment at different facilities.”	PN
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?	It is possible. Compliance was not assessed/reported. Participants were expected to use the device 24 hours per day for 90 days (30 days for the primary outcome). Given that these were all patients living in nursing homes, it is assumed that there was a relatively low risk of non-compliance.	PN
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Not reported. There is no suggestion that any data were missing, or that any patients were withdrawn from the study.	NI

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Highly unlikely. CFU count is an objective measure which is reported by a laboratory.	PN

4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Analyses were planned and documented in advance.	N
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	An objective measure was used.	N
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The analytic approach was described in the study protocol.	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	The primary endpoint was specified in the trial protocol as "the difference (compared with baseline) in laboratory measurement of bacterial colonization of the indwelling urinary catheter after 30 days of using UroShield". There were alternative options for the primary endpoint which could have been selected, including different time points (60 or 90 days), and number of infections. The latter would have been preferable (being a clinical outcome rather than a proxy measure), but in this study would have been underpowered.	N
5.3 ... multiple eligible analyses of the data?	As above. It might have been preferable to perform a repeated-measures analysis (rather than t-tests), to reduce the risk of multiplicity causing a type 1 error. However, the authors did pre-specify their selection of the 30-day primary outcome measure. As this is the key outcome, if taking that single analysis in isolation, a	N

	between-samples t-test may have been appropriate (assuming the data were normally distributed).	
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement	The risk of bias for this outcome measure is generally low. Some key details have not been reported by investigators, and it has been necessary to make some assumptions based on implied information. Our main concern is the absence of any reported baseline differences between groups. It is also worth noting that changing CFU counts may not directly correspond with clinical effectiveness of the device.	Low
Optional: What is the overall predicted direction of bias for this outcome?		Unpredictable

JBI Critical Appraisal Checklist for Case Series

Reviewer Sarah Kotecha Date 12/8/21

Author Da Silva Year 2021 Record Number

		Yes	No	Unclear	Not applicable
1.	Were there clear criteria for inclusion in the case series?	☐	☐	X	☐
2.	Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	X	☐	☐
3.	Were valid methods used for identification of the condition for all participants included in the case series?	☐	X	☐	☐
4.	Did the case series have consecutive inclusion of participants?	☐	☐	X	☐
5.	Did the case series have complete inclusion of participants?	☐	X	☐	☐
6.	Was there clear reporting of the demographics of the participants in the study?	☐	X	☐	☐
7.	Was there clear reporting of clinical information of the participants?	☐	X	☐	☐
8.	Were the outcomes or follow up results of cases clearly reported?	X	☐	☐	☐
9.	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	X	☐
10.	Was statistical analysis appropriate?	X	☐	☐	☐

Comments (Including reason for exclusion)

1. Criteria for inclusion not completely clear. The paper states the following "were provided with the devices and monthly consumables for their 'worst affected patients'." And then goes on to say "The clinical teams at each site identified adult patients with repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 more UTIs in the last 12 months (European Association of Urology, 2017) and where they had exhausted all other avenues." The other avenues where not specified further.

2. Results were self-reported by the patients.

3. As 2

4. No statement about whether or not the patients included were consecutive.

5. They recruited 29 patients but there only results for 23 patients included, reasons for this were given "During the evaluation, 2 patients passed away from other healthcare complications and four others withdrew for various medical reasons."

6. No demographics were given for the included patients.

7. Only information on UTIs etc. given, no other information on medical conditions.

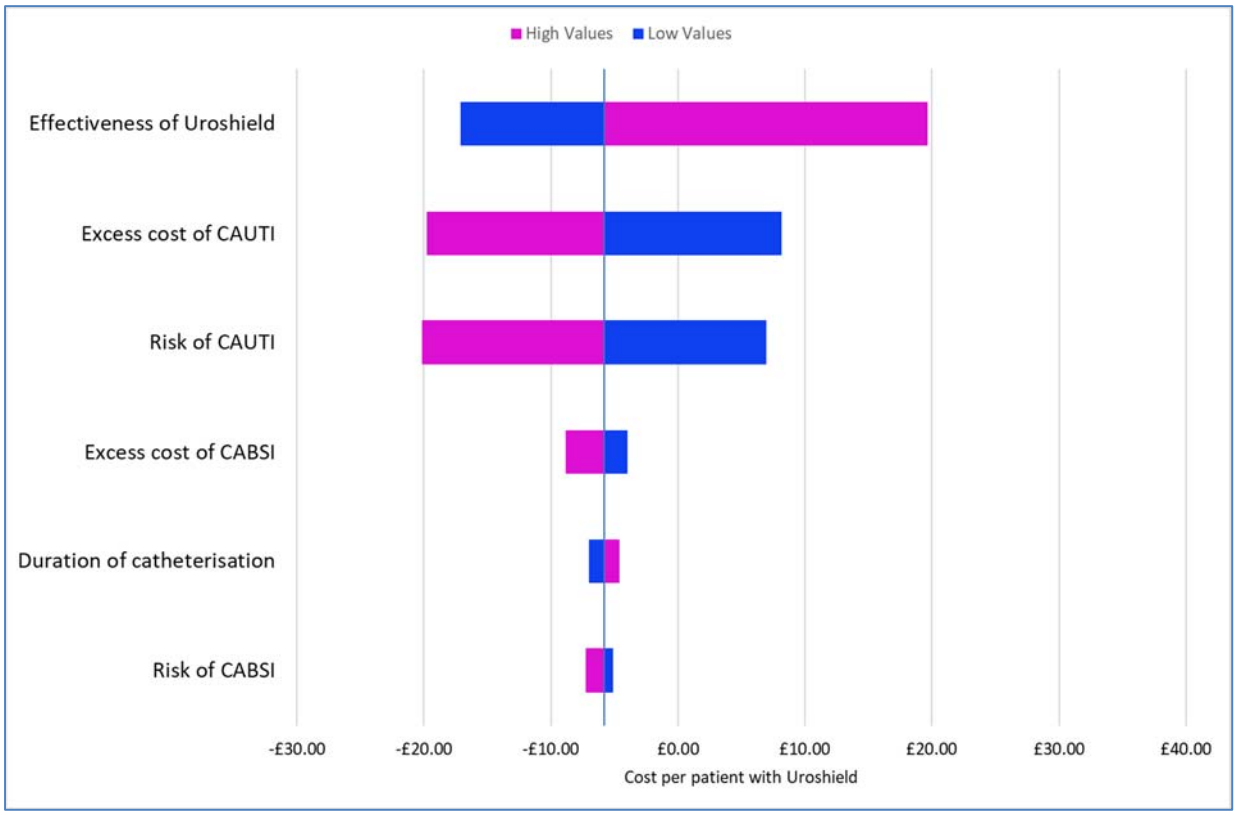
8. Outcomes were clearly reported.

9. Gives the following information "we had engagement from the following trusts: Frimley Park Hospital, Broomfield Hospital, Northampton Community Team; Worcester Community Team, St. James's Hospital and Pinderfields Hospital Spinal Injury Unit." But no other information is provided.

10. Statistical analysis was appropriate.

Appendix D – Sensitivity analysis, Tornado diagrams

Figure 5: Hospital all - company Tornado (top), EAC Tornado (bottom)



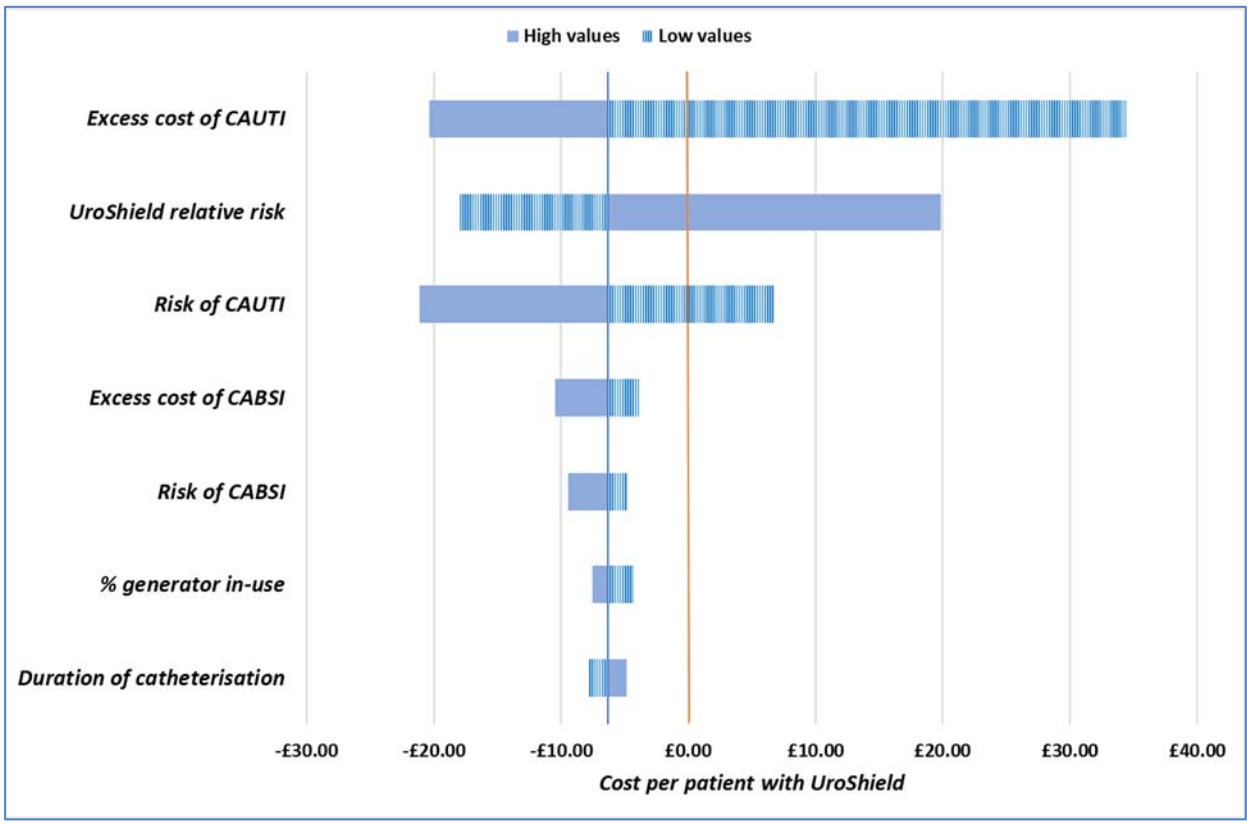
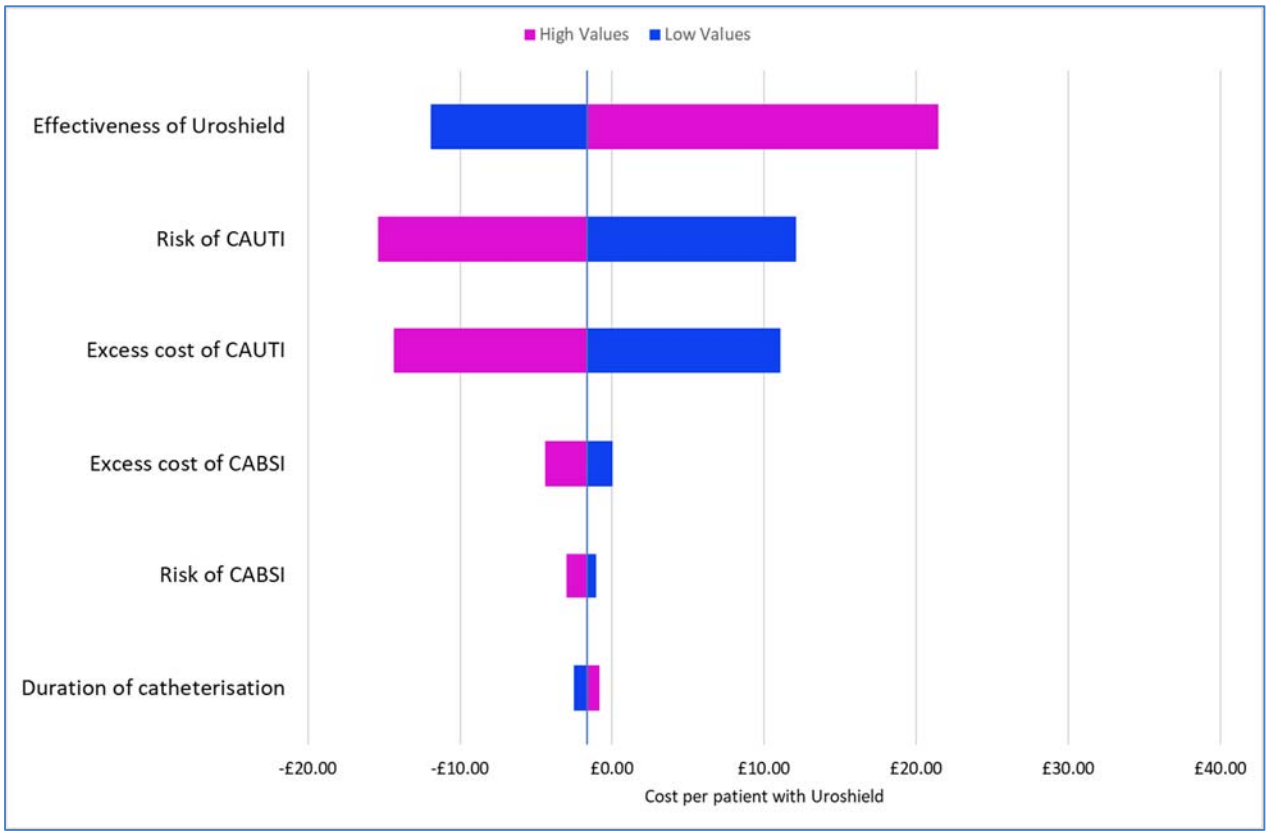


Figure 6: Hospital ≤28 days - company Tornado (top), EAC Tornado (bottom)



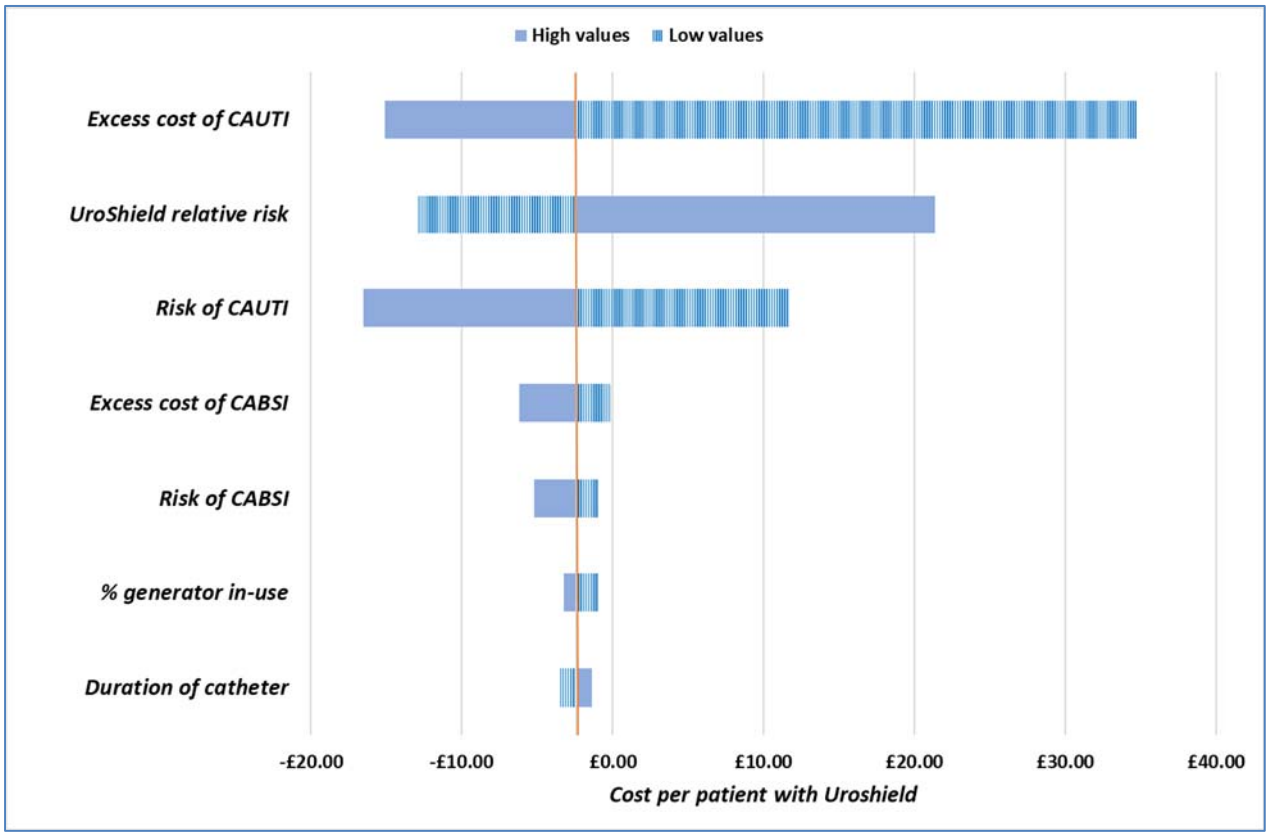


Figure 7: Hospital >28 days - company Tornado (top), EAC Tornado (bottom)

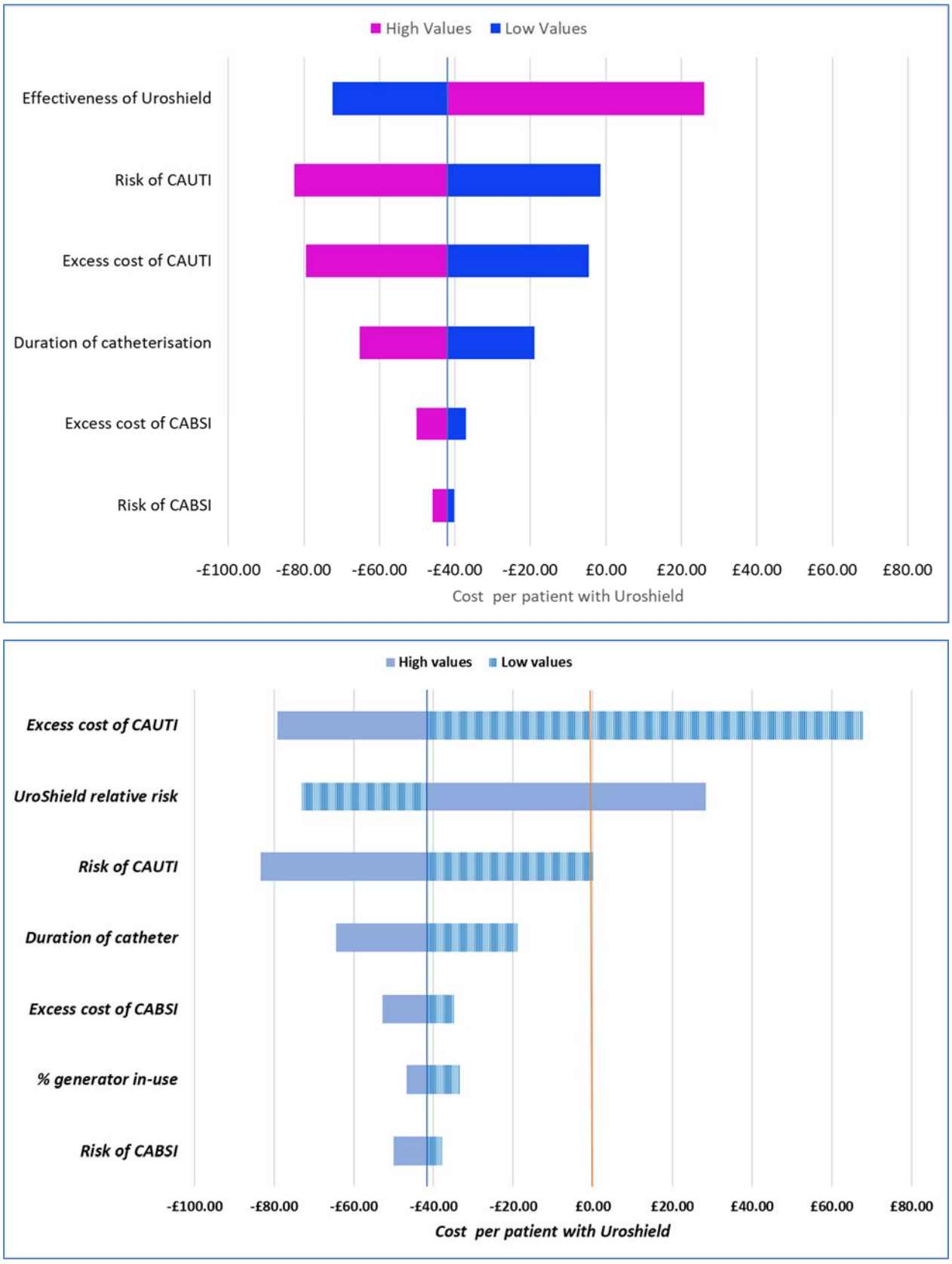
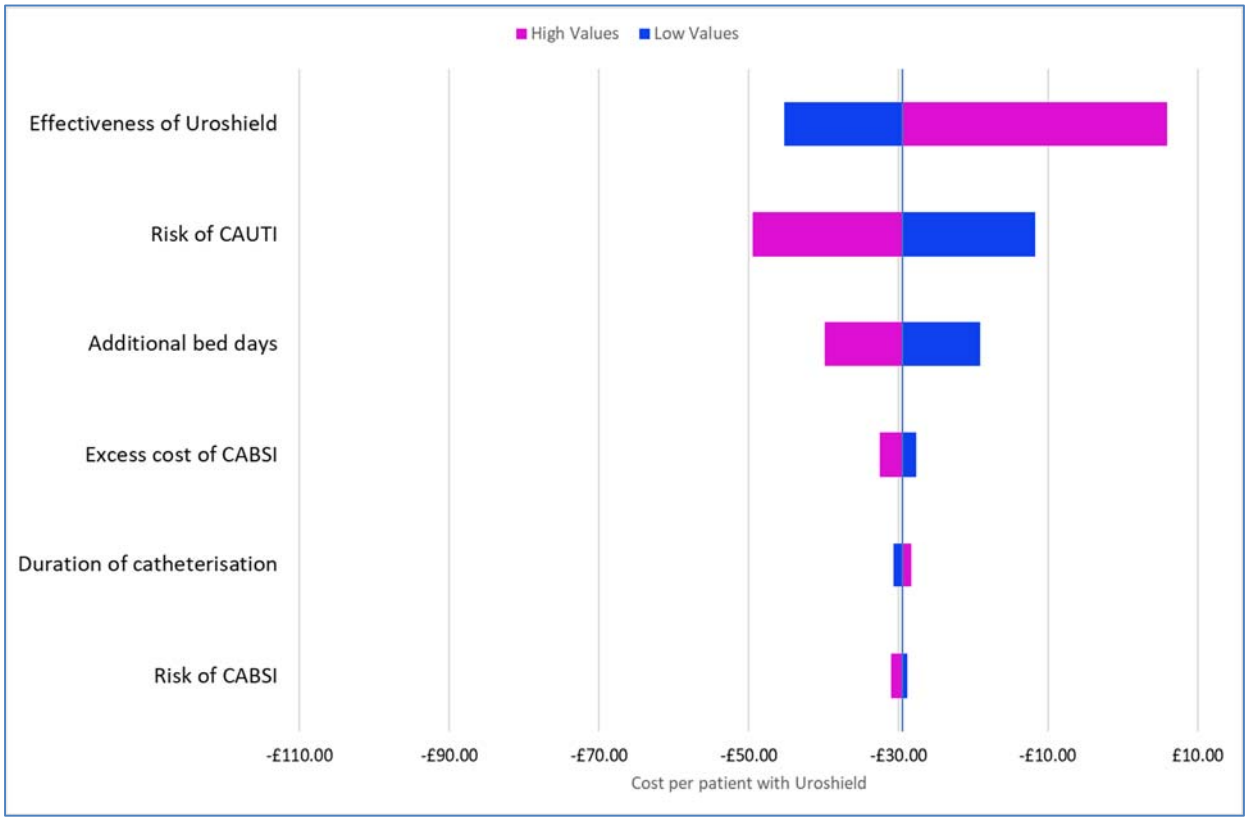


Figure 8: Hospital ICU - company Tornado (top), EAC Tornado (bottom)



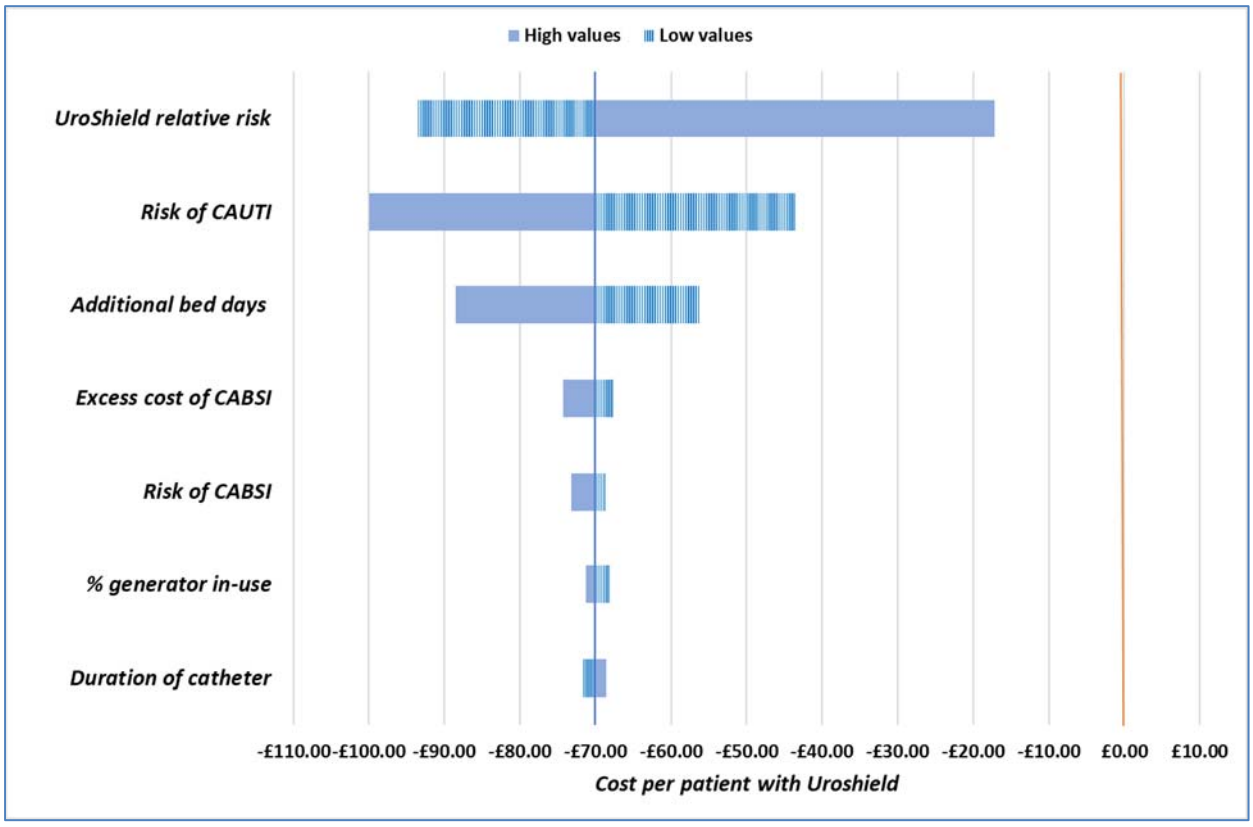
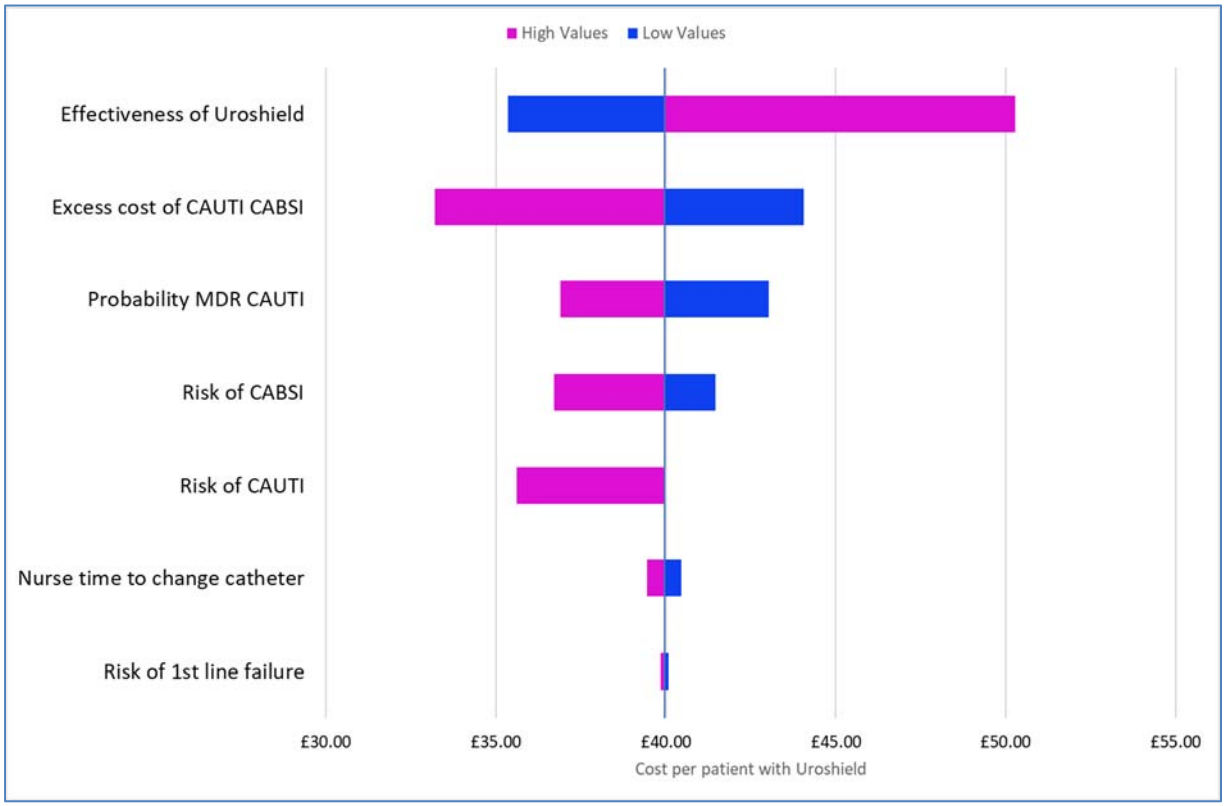


Figure 9: Community (all) - company Tornado (top), EAC Tornado (bottom – note change of scale)



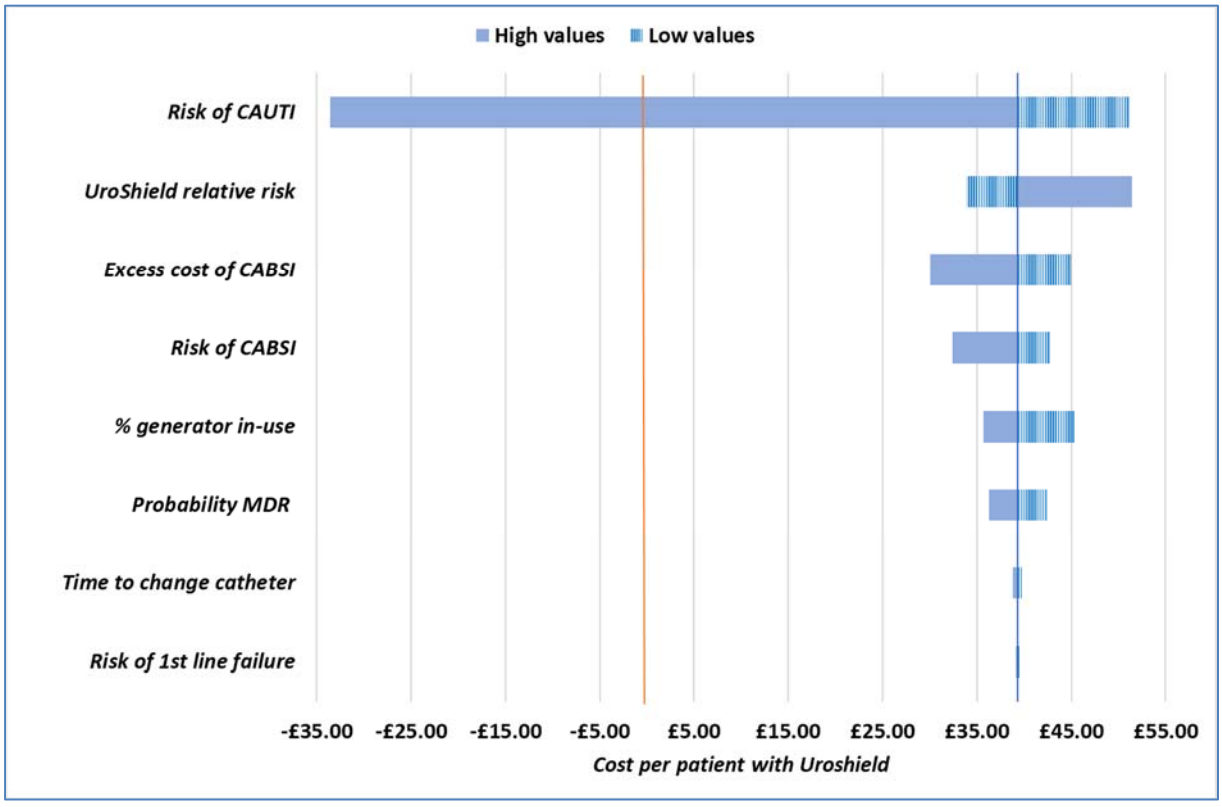
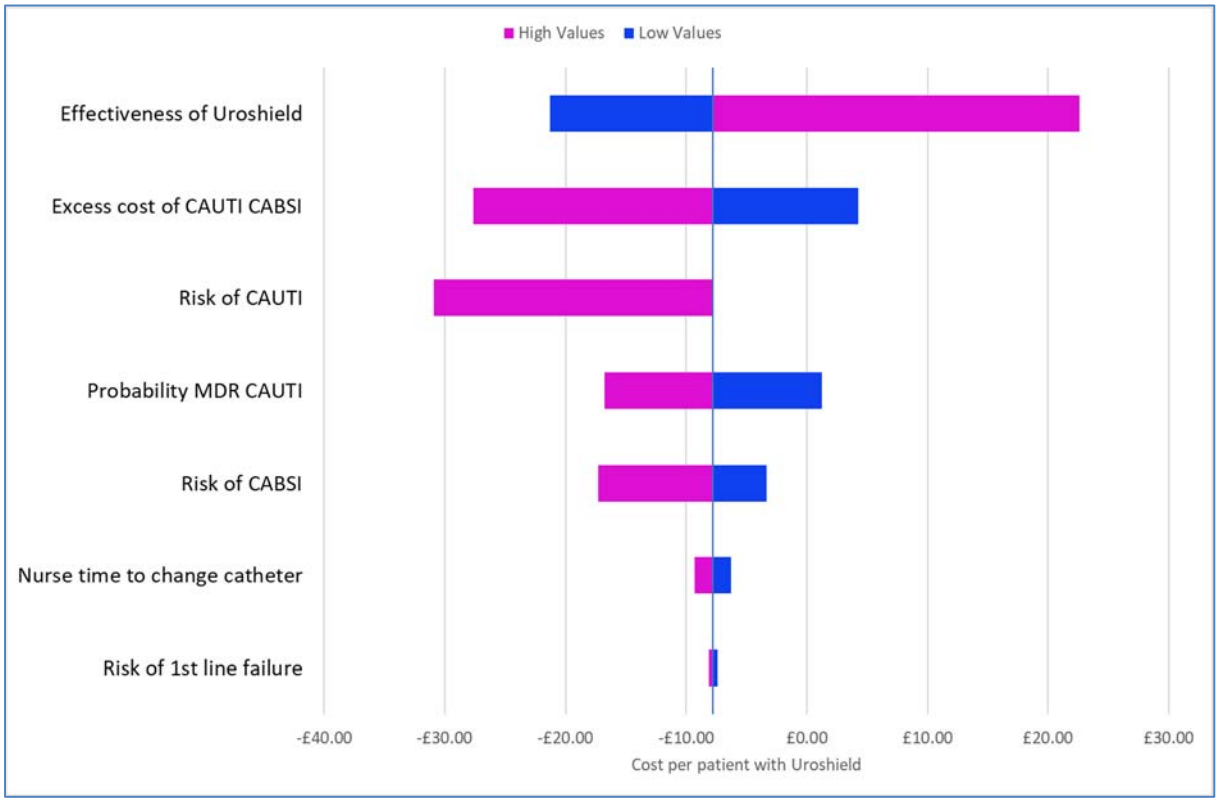


Figure 10: Community recurrent - company Tornado (top), EAC Tornado (bottom – note slight change of scale)



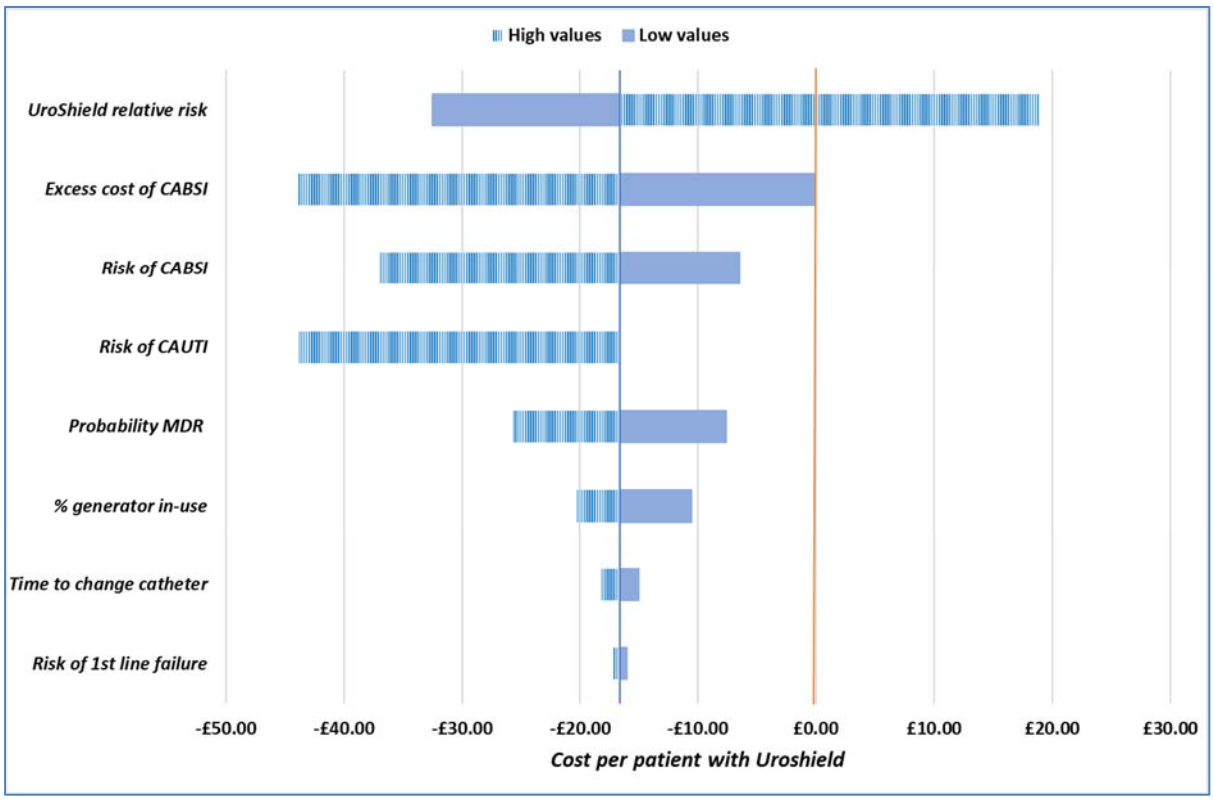


Table 19:Two-way sensitivity analysis: UroShield vs CAUTI risk, EAC model (base case values highlighted)

CAUTI Rate	Effectiveness of UroShield (risk reduction)										
	0.1	0.15	0.2	0.252	0.3	0.35	0.4	0.45	0.5	0.55	0.6
Hospital all											
0.030	-£3.22	£0.07	£3.36	£6.78	£9.93	£13.22	£16.51	£19.80	£23.09	£26.38	£29.67
0.035	-£13.09	-£9.25	-£5.41	-£1.42	£2.26	£6.10	£9.93	£13.77	£17.61	£21.44	£25.28
0.038	-£19.01	-£14.84	-£10.67	**-£6.34**	-£2.34	£1.82	£5.99	£10.15	£14.32	£18.48	£22.65
0.045	-£32.82	-£27.89	-£22.95	-£17.82	-£13.09	-£8.15	-£3.22	£1.71	£6.65	£11.58	£16.51
0.050	-£42.68	-£37.20	-£31.72	-£26.02	-£20.76	-£15.28	-£9.80	-£4.32	£1.16	£6.65	£12.13
Hospital – short stay (≤28 days)											
0.0250	£4.85	£7.59	£10.33	£13.18	£15.82	£18.56	£21.30	£24.04	£26.78	£29.52	£32.26
0.0300	-£5.01	-£1.72	£1.56	£4.98	£8.14	£11.43	£14.72	£18.01	£21.30	£24.58	£27.87
0.0345	-£13.89	-£10.11	-£6.33	**-£2.40**	£1.24	£5.02	£8.80	£12.58	£16.36	£20.15	£23.93
0.0400	-£24.75	-£20.36	-£15.98	-£11.42	-£7.21	-£2.82	£1.56	£5.95	£10.33	£14.72	£19.10
0.0450	-£34.61	-£29.68	-£24.75	-£19.62	-£14.88	-£9.95	-£5.01	-£0.08	£4.85	£9.79	£14.72
Hospital – long stay (>28 days)											
0.075	-£22.89	-£14.67	-£6.45	£2.10	£9.99	£18.22	£26.44	£34.66	£42.88	£51.10	£59.33
0.085	-£42.62	-£33.31	-£23.99	-£14.30	-£5.35	£3.97	£13.28	£22.60	£31.92	£41.24	£50.56
0.095	-£62.36	-£51.94	-£41.53	-£30.70	-£20.70	-£10.29	£0.13	£10.54	£20.96	£31.37	£41.79
0.1017	-£75.58	-£64.43	-£53.28	**-£41.69**	-£30.98	-£19.83	-£8.68	£2.46	£13.61	£24.76	£35.91
0.115	-£101.82	-£89.21	-£76.61	-£63.50	-£51.39	-£38.79	-£26.18	-£13.57	-£0.97	£11.64	£24.25
0.125	-£121.55	-£107.85	-£94.15	-£79.90	-£66.74	-£53.04	-£39.34	-£25.63	-£11.93	£1.77	£15.48
Hospital - ICU											
0.03	-£63.81	-£57.15	-£50.50	-£43.58	-£37.19	-£30.54	-£23.88	-£17.23	-£10.57	-£3.92	£2.74
0.035	-£83.77	-£76.01	-£68.25	-£60.17	-£52.72	-£44.95	-£37.19	-£29.43	-£21.66	-£13.90	-£6.13
0.038	-£95.75	-£87.32	-£78.89	**-£70.13**	-£62.03	-£53.60	-£45.18	-£36.75	-£28.32	-£19.89	-£11.46
0.045	-£123.70	-£113.72	-£103.74	-£93.36	-£83.77	-£73.79	-£63.81	-£53.83	-£43.84	-£33.86	-£23.88
0.05	-£143.66	-£132.57	-£121.48	-£109.95	-£99.30	-£88.21	-£77.12	-£66.03	-£54.94	-£43.84	-£32.75
Community - all											
0.050	£47.77	£48.90	£50.04	£51.21	£52.30	£53.44	£54.57	£55.70	£56.84	£57.97	£59.11
0.085	£33.48	£35.41	£37.34	**£39.34**	£41.19	£43.12	£45.05	£46.97	£48.90	£50.83	£52.76
0.150	£6.95	£10.35	£13.75	£17.29	£20.56	£23.96	£27.36	£30.76	£34.16	£37.56	£40.96
0.200	-£13.46	-£8.92	-£4.39	£0.33	£4.68	£9.22	£13.75	£18.29	£22.82	£27.36	£31.89
0.250	-£33.87	-£28.20	-£22.53	-£16.63	-£11.19	-£5.52	£0.15	£5.82	£11.49	£17.15	£22.82
0.300	-£54.28	-£47.47	-£40.67	-£33.60	-£27.07	-£20.26	-£13.46	-£6.66	£0.15	£6.95	£13.75
Community - recurrent											
0.15	£6.95	£10.35	£13.75	£17.29	£20.56	£23.96	£27.36	£30.76	£34.16	£37.56	£40.96
0.20	-£13.46	-£8.92	-£4.39	£0.33	£4.68	£9.22	£13.75	£18.29	£22.82	£27.36	£31.89
0.25	-£33.87	-£28.20	-£22.53	-£16.63	-£11.19	-£5.52	£0.15	£5.82	£11.49	£17.15	£22.82
0.30	-£54.28	-£47.47	-£40.67	-£33.60	-£27.07	-£20.26	-£13.46	-£6.66	£0.15	£6.95	£13.75
0.35	-£74.69	-£66.75	-£58.81	-£50.56	-£42.94	-£35.00	-£27.07	-£19.13	-£11.19	-£3.25	£4.68

UroShield – addendum on blockages and bacteriuria threshold

1 Blockages

The Lead Team raised the issue of UroShield reducing the need for catheter changes due to blockages, as a separate outcome to the reduction in CAUTIs. The clinical experts indicated that blockages are caused by the presence of a bacterial community, which changes the chemical environment of the urine. Patients may have a blockage without sign or symptom of a CAUTI, but these also require a change of catheter. One clinical expert indicated that 30% of unscheduled callouts for District Nurses are due to catheter blockages or bypass, and that there are some patients for whom this is a frequent event. The EAC was requested to investigate whether the effect on blockages could be added to the economic model.

The only report of the effect of UroShield on blockages is da Silva et al (2021). They report statistically significant reductions in UTIs, blockages, and catheter changes in patients with recurrent UTIs in the community following use of UroShield. Patients (n=22) used the device for 5-17 weeks and self-reported the number of events for the 30 days prior to use and the final 30 days of use. Note that the paper reports that the data are not normally distributed, so the mean values should be treated with caution. It is likely that a small number of patients with very frequent events have skewed the values upwards (i.e. 'typical' values are actually lower than those presented).

Mean events per 30 days	Baseline (SD)	Post-UroShield (SD)
UTI	3.24 (± 3.42)	0.5 (± 0.91)
Blockage	2.59 (± 3.75)	0.36 (± 0.91)
Catheter change	2.91 (± 3.57)	0.32 (± 0.48)

There is nothing to identify whether reported UTIs and blockages were co-existing or independent events. It is likely that there is some overlap in the events, but we cannot determine how many blockages occurred *in addition* to the UTIs. Of interest, the baseline rate of catheter change is slightly lower than the rate of UTIs, suggesting that not all UTIs resulted in a catheter change. These results *do* suggest that UroShield has a similar effect on the frequency of blockages to that on UTIs. The similar rates of UTI, blockage, and catheter change make it difficult to estimate how many catheter changes are required only for blockages.

The EAC conducted a rapid literature search for blockages and CAUTIs. Additional information on the rates of CAUTIs and blockages was found in Wilde et al (2017)[1], which indicated that a subset of long-term catheter users (34%) had blockages (self-reported). Some of these patients had very frequent blockage events, but there was no data that could estimate the risk of blockage in addition to the risk of CAUTI.

[1] Wilde MH, McMahon JM, Crean HF, Brasch J. Exploring relationships of catheter-associated urinary tract infection and blockage in people with long-term indwelling urinary catheters. Journal of clinical nursing. 2017 Sep;26(17-18):2558-71.

Recurrent CAUTI community population: In the EAC model, the recurrent CAUTI population has a baseline cost saving of £16.63 for UroShield. If we add additional treatment costs (District Nurses changing catheters due only to blockages), this means UroShield becomes more cost-saving. However, we have no data to indicate how many additional catheter changes would be avoided.

All Community population: The same is true for the 'All Community' population – we do not have data to say how many more catheter changes solely for blockages might be prevented by UroShield. In this population the base case is £39.34 cost-incurring. The cost of a catheter change (catheter cost + 15 min of nurse time) is £28.12. If we assume equivalent effectiveness of UroShield on blockages as for CAUTIs (as suggested by the da Silva data) the risk of blockage at which the base case for UroShield becomes cost-neutral is 1.87 per patient per 30 days. That is, a risk of CAUTI of 8.5% plus a risk of blockage of 187%. The two-way sensitivity analysis below shows how the base case result alters with a range of CAUTI and blockage risks. For patients at high risk of CAUTI UroShield is always cost saving. UroShield is also cost saving for patients who don't get CAUTIs but do get 3 or more blockages that require a catheter change.

	Blockage risk											
CAUTI risk	0.5	0.75	1.0	1.25	1.5	1.87	2.0	2.25	2.5	2.75	3.0	3.25
0.00	£57.66	£52.40	£47.14	£41.88	£36.63	£28.84	£26.11	£20.85	£15.59	£10.33	£5.08	-£0.18
0.05	£40.70	£35.44	£30.18	£24.92	£19.66	£11.88	£9.15	£3.89	-£1.37	-£6.63	-£11.89	-£17.14
0.085	£28.82	£23.57	£18.31	£13.05	£7.79	£0.01	-£2.73	-£7.98	-£13.24	-£18.50	-£23.76	-£29.02
0.15	£6.77	£1.52	-£3.74	-£9.00	-£14.26	-£22.04	-£24.78	-£30.04	-£35.29	-£40.55	-£45.81	-£51.07
0.20	-£10.19	-£15.45	-£20.71	-£25.96	-£31.22	-£39.00	-£41.74	-£47.00	-£52.26	-£57.51	-£62.77	-£68.03
0.25	-£27.15	-£32.41	-£37.67	-£42.93	-£48.18	-£55.97	-£58.70	-£63.96	-£69.22	-£74.48	-£79.74	-£84.99
0.30	-£44.11	-£49.37	-£54.63	-£59.89	-£65.15	-£72.93	-£75.66	-£80.92	-£86.18	-£91.44	-£96.70	-£101.96

2 Bacteriuria definition

The question was also raised about the effect of reducing the number of bacterial colonies used to define bateriuria. This is due to some patients becoming symptomatic at much lower bacterial loads than those used in the definition of bateriuria in the UroShield studies. This cannot be investigated in the economic modelling without additional data. The effectiveness of UroShield is based on the definitions of bacteriuria used in the studies. If the definition is changed we cannot predict the change in effectiveness. Bacteriuria is already a proxy outcome for the more useful outcome of 'CAUTI requiring treatment' (or similar). For economic modelling, it is the frequency of treatment that is important, not necessarily the reason for that treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

UroShield for preventing catheter-associated urinary tract infections

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Patient survey
- Appendix E: Decision problem

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1 The technology

UroShield (NanoVibronix) is an ultrasound device designed to reduce the risk of catheter associated urinary tract infection (CAUTI) by reducing bacterial colonisation and biofilm formation on indwelling urinary catheters. The technology works by generating low intensity 90kHZ ultrasonic surface acoustic waves which propagate throughout the catheter's entire length on both its inner and outer lumens. The company claims the acoustic waves interfere with the attachment of bacteria and formation of the biofilm. The company also claims the same acoustic waves reduce friction between the catheter and the person's internal tissues, thereby decreasing the pain, discomfort, and spasm associated with indwelling urinary catheters.

UroShield includes 2 components:

- A driver (battery or AC powered portable unit) which provides the power
- Single use actuator which is clipped to the external portion of any indwelling urinary catheter and generates ultrasonic waves.

UroShield can be used with catheters made of any material and size ranging from 12 to 22 French Gauge (FG). UroShield is to be worn continuously. The life expectancy of the driver is 2 years while the actuator should be replaced every 30 days. If the catheter is replaced within a 30-day period, the actuator can be removed and reattached to the new catheter.

UroShield is a CE marked class IIa medical device. UroShield is not intended for use in children. It is not intended as a treatment for an active urinary tract infection. It is not MRI compatible and should be removed from the catheter before entering an MRI suite. Uroshield 3.0 is the current version available in the NHS. The EAC confirmed that none of the refinements to the device since its launch in 2015 include a change to the mechanism of action or are likely to impact on clinical outcomes.

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2 Proposed use of the technology

2.1 Disease or condition

Indwelling catheters may be used short term (28 days or less) or long term (more than 28 days) (NICE 2017; Loveday et al. 2014). Around half of the people who have long-term catheters have problems such as pain, tissue damage, decreased mobility, and hospital attendances associated with blockage (Khan et al. 2007). A study estimated that over 90,000 people in the UK had long-term catheters in the community (Gage et al. 2017). People with indwelling urinary catheters are at risk of developing CAUTI, with increased risk for every day the catheter is in place. CAUTI is defined as the presence of symptoms or signs compatible with a urinary tract infection (UTI) in people with a catheter with no other identified source of infection plus significant levels of bacteria in the catheter or midstream urine specimen when the catheter has been removed within the previous 48 hours (NICE 2018).

UTI accounted for 19% of healthcare-associated infections, with 43% to 56% of UTIs associated with a urethral catheter (Loveday et al. 2014). The prevalence of CAUTI in people with catheters in community settings was 8.5% (Getliffe and Newton, 2006). Smith et al. (2019) estimated that approximately 3.8% of inpatients with catheters in the UK developed hospital-onset CAUTI. Rates of CAUTI increased with length of stay, ranging from 3.1% in people in hospital for 2 days to 13% in those who stayed for 40 days or more. Approximately 4.8% of inpatients with CAUTI developed hospital-onset catheter associated blood stream infection (CABSI).

2.2 Patient group

UroShield is intended to reduce the risk of CAUTI in people with indwelling urinary catheters. This guidance considers the use of UroShield in both hospital and community care settings.

2.3 Current management

NICE's healthcare-associated infections guideline states that the risk of blockages, encrustations, and catheter-associated infections in long-term

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urinary catheters should be minimised through patient-specific regimens. These include reviewing the frequency of planned catheter changes, increasing fluid intake, and documenting catheter blockages. Bladder instillations or washouts should not be used to prevent catheter-associated infections. Catheters should be changed only when clinically necessary or according to the manufacturer's recommendations. Prophylactic antibiotics should not be used routinely for catheter changes. These should only be considered for people who have a history of symptomatic UTI after catheter change or who experience trauma during catheterisation.

Healthcare professionals play a key role in caring for people with indwelling urinary catheters and reducing CAUTI. The doctor, specialist nurse, or district nurse decides whether a person needs a catheter and how it should be managed based on the individual's needs. The Royal College of Nursing's catheter care guidance for healthcare professionals covers aspects of catheter care such as documentation, risk assessment, and review. In England, urinary catheter tools such as a catheter passport, catheter card, and inpatient care plan have been used to allow healthcare professionals to document catheter care and share information between care services.

NICE's public health guideline on healthcare-associated infections states that hospital trusts regularly review evidence-based assessments of new technologies and other innovations to minimise harm from healthcare associated infections and antimicrobial resistance.

2.4 Proposed management with new technology

UroShield is an add-on to standard of care. The company proposes that UroShield would be offered for:

- people with a high risk of developing CAUTI who need long-term urinary catheters in primary or community care
- people with a high risk of developing CAUTI who need urinary catheters for more than 48 hours in secondary care

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- people with recurrent infections (2 or more CAUTI in the past 6 months or 3 CAUTI in 1 year) who need urinary catheters

The EAC considered that the use of UroShield would not substantially change the management pathway. It noted that the term 'high risk' was not definitively described in the company's submission, although the company suggested several parameters that might contribute to this consideration. These included: biological sex, history of urinary tract problems, neurologic conditions causing neurogenic bladder problems, previous UTIs, previous or current abnormal voiding patterns, catheter history, incontinence, comorbid conditions such as diabetes, and immunosuppression.

The clinical experts agreed that the benefits of UroShield would most likely be observed in community and primary care settings. People who need long-term catheterisation at high-risk of CAUTI, including those with previous recurrent infections, would be most likely to benefit from the technology.

UroShield would typically be set up by healthcare professionals who insert catheters. The company states that after some training, many patients and carers can manage and care for the device themselves.

3 Company claimed benefits and the decision problem

The company's claimed benefits and the decision problem are described in Appendix E. The company has not proposed any changes to the scope.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 7 studies from a systematic search and presented them in the submission. The EAC did its own search and identified 13 publications describing 8 studies relevant to the decision problem. The 8 studies included the 7 studies described in the company submission and a

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case series in Turkish (Turan et al. 2012). Table 1 presents the studies included in the company submission and EAC assessment.

Table 1: Publications in the company submission and the assessment report.

Studies included by both EAC and company	
Publication and study design	7 studies: • 1 RCT (Markowitz et al. 2018) • 1 before-and-after study (da Silva et al. 2021) • 2 company reports (Zalut 2007 (unpublished), Zillich et al. 2014) • 2 conference abstracts or posters (Ikinger et al. 2007, Nagy et al. 2011) • 1 clinical trial report (Shenfeld and Haris 2010) (unpublished)
Publications not in company submission included by EAC	
Publication and study design	1 case series (Turan et al. 2012). Paper in Turkish translated by the company
Additional publications on studies in company submission	• 3 conference abstracts or posters (Rosenblum 2017 reported in Markowitz et al. 2018], Zillich et al. 2008 reported in Ikinger et al. 2007], Zillich et al. 2014 [reported in Zillich et al. 2014]) • 1 study protocol (Markowitz 2018 [reported in Markowitz et al. 2018]) • 1 baseline patient data submitted via email at EAC request (da Silva et al. 2021 [reported in da Silva et al. 2021]).

There were 3 peer-reviewed publications on UroShield (da Silva et al. 2021, Markowitz et al. 2018, Turan et al. 2012). Markowitz et al. (2018) reported data from a double-blinded randomised controlled trial which compared UroShield with a sham device in 55 people in nursing homes in the US. The EAC assessed this study to have an overall low risk of bias (Cochrane Risk of Bias Assessment Tool). da Silva et al. (2021) is a before-and-after study which the EAC appraised using the Joanna Briggs Institute critical appraisal checklist for case series.

The EAC did not formally appraise the quality of the remaining studies because of a lack of detail about study design and methods. The EAC commented on some limitations of these studies, and these are summarised in Table 2.

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The results of the included studies and reports are presented in Table 2 and summarised here.

Bacterial load or bacteriuria (colony forming units)

Three studies showed UroShield resulted in significantly less bacteriuria than comparators (Markowitz et al. 2018, Nagy et al. 2011, Zillich et al. 2014) but 2 studies reported no statistically significant difference (Ikinger et al. 2007, Shenfeld and Haris 2010). The most significant improvement was seen in people with long-term indwelling urinary catheterisation (Markowitz et al. 2018).

The company did a meta-analysis including 4 studies to estimate the effect of UroShield on bacteriuria (more than 10,000 CFU per ml) (Markowitz et al. 2018, Nagy et al. 2011, Shenfeld and Haris 2010, Zillich et al. 2014). The company meta-analysis found the pooled risk ratio for bacterial infection was 0.25 (95% confidence interval 0.11 to 0.57) in favour of UroShield. This indicates a potential 75% reduction in bacterial infection with UroShield compared with comparators. The EAC considered the meta-analysis to have several limitations related to the quality of the studies included and the generalisability of findings to the NHS. However, it agreed with the rationale for including these studies and the methodological approach used by the company. The EAC re-ran the meta-analysis and reported a pooled risk ratio of 0.27 (0.12 to 0.57). This slight difference from the company's meta-analysis is because of the different statistical software used to perform the calculations.

Urinary tract infection (UTIs) or antibiotic use

People using UroShield had fewer new UTIs requiring antibiotics than those using the sham devices (Markowitz et al. 2018) and had fewer UTIs after approximately 12 weeks of use compared with baseline (da Silva et al. 2021). Nagy et al. (2011) found no symptomatic UTIs in either treatment arms. da Silva et al. (2021) also found a reduction in antibiotics use with the use of UroShield compared with baseline (mean 0.8, standard deviation, SD=1.1 versus 2.1, SD=2.3, p=0.009).

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Catheter blockages or unplanned catheter changes

da Silva et al. (2021) reported significantly fewer catheter blockages and unplanned catheter changes after long-term use of UroShield (range 5 to 17 weeks).

Pain or discomfort

People who used UroShield reported lower levels of pain (da Silva et al. 2021, Shenfeld and Haris 2010, Zalut 2007), discomfort (Shenfeld and Haris 2010), spasm (Shenfeld and Haris 2010, Zalut 2007), and itching and burning (Zalut 2007) compared to baseline or comparators. People using UroShield also reported fewer catheter-related complaints (Nagy et al. 2011) and improved wellbeing (Zalut 2007).

Patient reported outcomes

Patient reported outcomes were reported narratively in 1 study (da Silva et al. 2021). Everyone who responded thought that UroShield was easy to use and beneficial. Fifty percent of people reported feeling happier about their urinary catheter and no one reported feeling worse. Positive outcomes reported included:

- Reduced risk and frequency of CAUTI
- More time between catheter changes
- Improved quality of life, with more socialisation and independence, and less worries about their condition

Some minor inconveniences were reported, including sediment build up in the catheter. Some people also made negative comments on the design of UroShield, related to battery life and discomfort in using the device at night.

Summary of clinical evidence

The EAC concluded that the evidence suggests that using UroShield could reduce the risk of bacteriuria and symptomatic UTIs in people with long-term catheters. It noted that the evidence for the benefit of UroShield in people with short-term catheters is very limited and does not suggest any clinical benefit at this time. It noted that the clinical evidence was limited in both quantity and

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quality. The EAC considered that studies done in community settings in people with previous UTI (Markowitz et al. 2018) or recurrent infections (da Silva et al. 2021) are likely to be most reflective of potential UK practice. The EAC concluded that although UroShield is safe and easy for patients and showed promise for the prevention of CAUTIs, there is not enough good quality evidence to support routine adoption at this time.

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Table 2: Details of the 8 studies included in the EAC assessment report

Study, design, and funding	Participants/ population	Intervention & comparator	Outcome measures and results	EAC comments
Long-term catheterisation (more than 28 days)				
Markowitz et al. (2018) RCT NCT03090373 Also reported in: Study protocol (US-2 Revision 2) Rosenblum (2017) Funding: company	55 adults (76% male, age 79.9±5) with long-term indwelling urinary or suprapubic catheters (>1 year) recruited from skilled nursing facilities in the US.	Intervention (n=29): UroShield with catheter for 30 days. Comparator (n=26): Sham device (which acted identically to the active devices, emitting a similar hum, but without emitting any Surface Acoustic Wave) with catheter for 30 days. All people were followed for another 60 days of standard of care.	**Significant improvement in bacterial load (colony forming units, CFU) between UroShield and sham from** • **baseline to 30 days** Mean improvement advantage of 87.2k CFU for UroShield compared with sham (p<0.001) • **baseline to 90 days** Mean improvement advantage of 79.3k CFU for UroShield compared to sham (<0.001) **Number of new UTIs requiring antibiotics** • **at 30 days** UroShield group=0 versus Sham group=7 • **within 90 days** UroShield=3 versus sham=14 (p=0.001)	Peer-reviewed study which is relevant to scope. Low risk of bias. Participants and investigators were blinded to treatment allocation. There is an uncertainty about group differences at baseline. Sample size was small and statistical multiplicity in the data analysis may have increased the risk of a Type 1 error
da Silva et al. (2021) Before-and-after study Funding: not reported	23 adults recruited via primary or secondary care in the UK who had 2 or more UTIs in the previous 6 months or 3 or more UTIs in the last 12	Intervention (n=23): UroShield with catheter for 5 to 17 weeks. Most people were on trial for 12 weeks 80% of people were taking antibiotics	**Change in number of UTIs** Reduction in mean number of UTIs (0.5±0.9) compared with baseline (3.2±3.4, p=0.001) **Use of antibiotics** Reduction in antibiotic treatment (0.8±1.1) compared with baseline (2.1±2.3, p=0.009) **Number of catheter blockages**	Peer-reviewed study which is relevant to scope. No reporting of demographic details and very limited or vague reporting of patient recruitment, previous

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	months and where all other treatment options were exhausted Note: 29 people were recruited, but 2 passed away from other health complications and 4 others withdrew for medical reasons.	while testing the device. Outcomes were calculated from the final 3 weeks of use and compared to baseline	Reduction in blockages (0.4±0.9) compared with baseline (2.6±3.8, p=0.006) **Number of unplanned catheter changes** Reduction in unplanned changes (0.3±0.5) compared with baseline (2.9±3.6, p=0.001) **Number of bladder washouts** No statistically significant reduction in bladder washouts (n=17, 0.7±1.7) compared with baseline (n=17, 2.7±6.0, p=0.104) **Visual Analog Scale for pain** Reduction in patient reported pain (n=20, 2.6±1.9) compared with baseline (n=21, 3.3±2.2; p=0.017)	treatments, and reasons for using UroShield Some additional details provided by the study author prior to the full study being published (see correspondence log)
Nagy et al. (2011) Comparative study Conference poster Funding: not reported	27 adults needing long-term catheterisation in Hungary	Intervention (n=14): UroShield with catheter Comparator (n=13): Urinary catheter alone Both groups were catheterised for 8 weeks	**Health condition** No symptomatic UTIs in either group **Significant bacteriuria (more than 100,000 CFU/ml) at 8 weeks** Four (33%) cases of bacteriuria in UroShield group compared with 9 (82%) in comparator **Rate of biofilm formation and encrustation assessed by scanning electron microscopy** One (8%) catheter had biofilm in UroShield group compared with 9 (82%) in comparator **Catheter-related complaints** Patient reported complaints score (scale 1 to 10) decreased in UroShield group (1.0 from 2.6) but increased in comparator (3.4 from 2.1) Catheter removed prematurely in 2 people in UroShield group (1 blockage, 1 bleeding) and 2 in comparator (1 balloon error, 1 bleeding)	Small sample size No description of treatment allocation criteria Level of significance of the differences in outcomes not reported
Short-term catheterisation (28 days or less)				

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Ikinger et al. (2007) A double blinded RCT Conference poster Also reported in: Zillich et al. (2008) conference poster Funding: not reported	22 adults with urological cancer in Germany	Intervention (n=11): UroShield with catheter Comparator (n=11): Sham device with catheter Average catheterisation was 9±2 days (range 5 to 13)	**Biofilm formation assessed using scanning electron microscopy** No catheters with biofilm in UroShield group compared with 7 (64%) in sham group. **Bacteriuria (not defined)** No statistical significance found between the 2 groups. **Adverse events (not detailed)** No differences in reported adverse event between groups	Authors claim it is the earliest clinical study of UroShield (conducted 2005-2006) Small sample size with limited demographic information No details on methods for randomisation or blinding. Not all outcomes are well defined
Shenfeld & Haris (2010) An open label RCT NCT00446732 Unpublished Funding: company	40 adults admitted to hospital needing urinary catheter for more than 24 hours in Israel	Intervention (n=27, 89% male, age 50±18.7): UroShield with urinary catheter Comparator (n=13, 77% male, age 52±14.5): Urinary catheter alone Treatment duration was up to 13 days	**Bacteriuria (only assessed to day 3)** No significant difference in bacteriuria at day 3 in UroShield group (1/19, 5%) compared with comparator (1/10, 10%; p=0.33). **Use of pain medication (for any condition)** 17 (63%) people in UroShield group received pain medication compared with 11 (85%) in comparator **Catheter-related complaints (scale 0 to 10)** Lower patient reported pain in UroShield group (2.2±2.7) than comparator (3.2±2.7, p=0.02) Lower reported discomfort in UroShield group (2.8±3.0) than comparator (4.0±3.3, p=0.01) Lower reported spasm in UroShield group (2.5±2.7) than comparator (3.6±3.2, p=0.01) **Serious adverse events and device-related adverse events** Eight (30%) adverse events reported in UroShield group and 10 (77%) in comparator. Only 1 serious adverse event reported which was in comparator	Reported in unpublished clinical trial report provided by company High risk of bias. Open label (unblinded) trial which was approved for n=210 but was closed early by the company Not powered to detect differences in tissue damage, catheter blockage or changes, UTIs, use of antibiotics, or presence of biofilm between the 2 groups. Potentially flawed sample-size rationale with risk of multiplicity (multiple t-tests). Analysis assumes data are normally distributed.

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			group. The adverse events are unlikely to be related to the devices.	
Zalut (2007) Case series Unpublished Funding: not reported	10 adults (mean age 63.5 years) discharged from emergency department with urinary catheter Location not known	Intervention (n=10): UroShield with urinary catheter Average use was 6.6 days (range 4 to 12)	**Daily questionnaire (scale 1 to 10) of pain, discomfort, and wellbeing up to day 4** Decrease in patient reported pain (mean 6.1 to 1.8), itching (mean 2.6 to 0.4), burning (mean 3.7 to 0.2), and spasm (mean 3.7 to 1.0) from baseline to day 4 Increase in patient reported wellbeing (mean 3.3 to 7.0) from baseline to day 4	Reported in unpublished company report No statistical analyses. Some conclusions not evidenced (tolerance and injuries)
Zillich et al. (2014) RCT Funding: not reported	40 adults needing urinary catheter after radical prostatectomy in Germany	Intervention (n=20 mean age 66.7 years): UroShield with urinary catheter plus single dose Ceftriaxon Comparator (n=20 mean age 60.7 years): Urinary catheter plus twice daily trimethoprim with post-operative dose Ceftriaxon on day 1-3 Average use for intervention was 8.4 days (7 to 12) Average use of comparator was 8.3 days (7 to 10)	**Bacteriuria (>1,000 CFU/ml)** One (5%) case of bacteriuria in UroShield group compared with 4 (20%) in comparator	No information provided on randomisation or blinding No statistical analyses Number of UTIs not reported Unsubstantiated conclusion of superiority.
Duration unknown				

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Turan et al. (2012) Case Series Funding: not reported	4 adults admitted to hospital needing catheterisation in Turkey	Intervention (n=4): UroShield with urinary catheter		Paper was originally in Turkish with English language translation provided by company This is a narrative report which is limited in detail on methods and results. No defined objectives, no clearly stated outcomes, and no statistical analysis. High risk of bias. Unblinded study with small sample size. All patients had different indications for catheterisation

Abbreviations
CFU, colony forming units; EAC, external assessment centre; NHS, National Health Service; RCT, randomised controlled trial; UTI, urinary tract infection

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4.2 Summary of economic evidence

The company and the EAC did not find any published economic evidence.

De novo analysis

The company submitted 2 simple decision tree models which compared the costs and health outcomes associated with using UroShield as an addition to standard of care in 6 different situations in hospital and community settings. The settings and populations considered were:

Hospital setting:

- All hospital patients
- Hospital patients with short-term catheterisation (28 days or less)
- Hospital patients with long-term catheterisation (more than 28 days)
- Patients in the intensive care unit (ICU)

Community setting:

- All community patients
- Community patients with recurrent UTI

The EAC considered the model structure and NHS perspective to be appropriate. It noted that these populations do not necessarily match those in the clinical literature and there was no evidence supporting use in the ICU. Different definitions are used for short- and long-term catheterisation.

Hospital settings had a time horizon of the duration of catheterisation or the duration of treatment for CAUTI. Community settings is presented as a rolling 30-day model with the same costs and benefits every 30 days.

The EAC considered the model structure in the hospital setting to be appropriate (see Figure 1). It considered that the company's description of the model in the community setting did not accurately represent the data, or the model used. The EAC considered that CABSI should be represented as an alternative to 2nd line treatment in those who did not respond to 1st line treatment (see Figure 2). It noted that this difference is entirely conceptual and has not altered the actual model.

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Figure 1: EAC diagram of hospital setting model (single arm only)

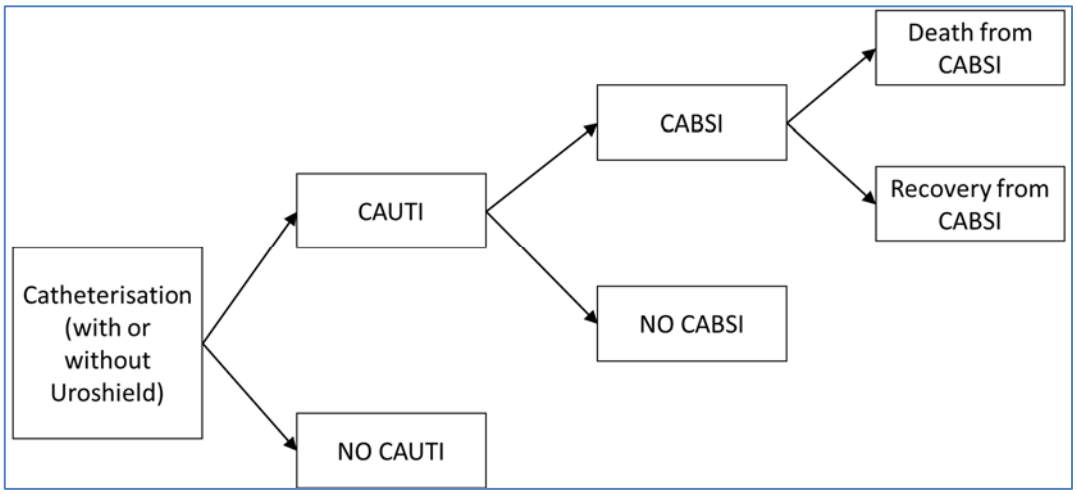
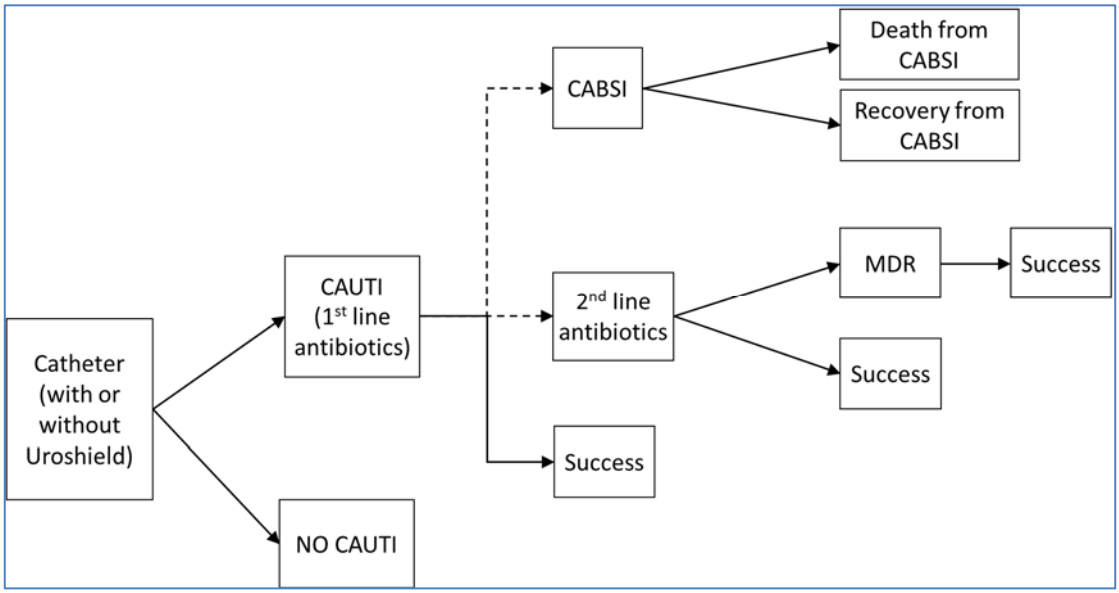


Figure 2: EAC diagram of community setting model (single arm only)



The EAC accepted all the assumptions made in the company's model. It identified some additional assumptions such as no long-term cost consequences to CAUTI or CABSI and no costs incurred by death (details are reported in Table 11 section 9.2 of the assessment report).

Model parameters

For the clinical parameters described in Table 12 in section 9.2 of the assessment report, the EAC agreed with most of the values used in the

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company's model, but it amended 2 parameters. The risk that CAUTI would progress to a CABSI was sourced from Smith et al (2019). The EAC used a value of 6.6% (with sensitivity range 5.0% to 9.8%) while the company used 4.8%.

In the company's model, 8% of people with infections in the community do not respond to 1st line treatment. However, the EAC changed this to 14% to include the 6% who have multi-drug resistant (MDR) infections.

Costs and resource use

The costs of UroShield include £349 for the driver and £50 per actuator (excluding VAT). The company estimated the cost of using UroShield was £0.48 per day based on an assumption that the driver would be used for 760 days over 2 years. The EAC considered that it was unlikely that the UroShield driver would be used every day, and it assumed 80% use of the 2-year lifespan (584 days over 2 years). Therefore, the cost of using UroShield was £0.60 per day in the EAC model.

The average cost of treating community CAUTI was £386.72 in the company's model. The EAC amended this to £454 to account for treatment failures and CABSI.

The company used a meta-analysis that reported the excess length of stay for people in ICU with CAUTI (Chant et al. 2011). The company used a cost of a bed day in ICU (£1,218) taken from 2018-19 Reference Costs. The EAC updated this using the 2019-20 Reference Cost data, which resulted in a daily ICU cost of £1,620. The EAC noted that this method was a conservative approach, which may underestimate the cost of CAUTI in ICU patients by not accounting for additional treatment requirements.

The mean cost per CAUTI was calculated from the cost per CAUTI per patient plus the cost of CABSIs for the proportion of patients where they occur. The company therefore calculated the mean cost per CAUTI in hospitals as £2,131 based on treatment costs and the occurrence of CABSI in 4.8% of patients. The company's mean cost per CAUTI in the ICU was £2,964 based on excess

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bed days and the proportion of patients developing CAUTI. In the EAC base case, these values were £2,192 and £4,436, respectively.

Results

Base case results

The company and the EAC base case results showed cost saving in all scenarios except for general community use, which would be around £40 cost incurring per person per month. The low cost of treating a community based CAUTI (£453.54) and the relatively low base rate of infection (8.5%) suggested that insufficient CAUTIs would be saved in this scenario to balance the cost of UroShield. For people with recurrent UTI in the community, the cost of CAUTI is the same, however the base rate of infection is much higher (25%) resulting in an overall cost saving per month (Table 3).

Table 3: Summary of base case results

	Company Submission			EAC Results		
	SoC	**UroShield**	**Cost saving per person**	**SoC**	**UroShield**	**Cost saving per person**
Hospital - all						
Cost of CAUTI	£80.99	£20.41	£60.58	£83.31	£21.00	£62.31
Other costs	£0	£54.78	-£54.78	£0	£55.98	-£55.98
Total cost	£80.99	£75.19	**£5.80**	£83.31	£76.97	**£6.34**
Hospital ≤28 days						
Cost of CAUTI	£73.53	£18.53	£55.00	£75.64	£19.06	£56.58
Other costs	£0	£53.35	-£53.35	£0	£54.18	-£54.18
Total cost	£73.53	£71.88	**£1.65**	£75.64	£73.24	**£2.40**
Hospital >28 days						
Cost of CAUTI	£216.75	£54.62	£162.13	£222.97	£56.19	£166.78
Other costs	£0	£120.08	-£120.08	£0	£125.10	-£125.10
Total cost	£216.75	£174.70	**£42.05**	£222.97	£181.29	**£41.69**
Hospital – ICU						
Cost of CAUTI	£112.66	£28.39	£84.27	£168.59	£42.48	£126.10
Other costs	£0	£54.78	-£54.78	£0	£55.98	-£55.98

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Total cost	£112.66	£83.17	**£29.49**	£168.59	£98.46	**£70.13**
Community – all						
Cost of CAUTI	£32.87	£8.28	£24.59	£38.55	£9.71	£28.84
Other costs	£0	£64.54	-£64.54	£0	£68.18	-£68.18
Total cost	£32.87	£72.83	**-£39.95**	£38.55	£77.89	**-£39.34**
Community – recurrent						
Cost of CAUTI	£96.68	£24.36	£72.32	£113.38	£28.57	£84.81
Other costs	£0	£64.54	-£64.54	£0	£68.18	-£68.18
Total cost	£96.68	£88.90	**£7.77**	£113.38	£96.75	**£16.63**

Sensitivity analysis

The company submitted one-way sensitivity analysis in the form of tornado diagrams. The parameters were varied by the ranges taken from the source or ±25% of the base values. Its results suggested that the effectiveness of UroShield is the key cost driver in all models.

The EAC amended the company's sensitivity ranges and added a parameter to account for the out-of-use time for the driver. The EAC also conducted a two-way sensitivity analysis for the risk of CAUTI and the effectiveness of UroShield in all 6 populations. The results suggested that as the risk of CAUTI increased, UroShield would be more likely to be cost-saving. Alternatively, as the effectiveness increased UroShield would be cost-saving in more populations.

In the EAC model, all combinations of effectiveness and infection risk in the ICU setting remained cost-saving. In the overall community setting, even if UroShield reduced CAUTI by 80-90% it would only be cost saving in populations where the rate of CAUTI was greater than 15-20%. In the community recurrent population, the lower value for CAUTI rate was extended down so that the definition of 'recurrent' infection starts at 1.8 per year, rather than 3 (as per the European Association of Urology definition).

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Number needed to treat results

The company did an additional analysis to determine the number of patients needed to treat (NNT) with UroShield to avoid one death. In the company's model this varied from 571 in the recurrent community population to 4,140 in the short-term hospital population. In the EAC model, this was reduced to 416 in the recurrent community and 3,011 in the short-term hospital populations. See table 17 in the assessment report for full details.

Summary of the economic evidence

The EAC concluded that UroShield is likely to be cost saving in populations with higher rates of CAUTI or higher treatment costs. This included hospital settings and community patients with recurrent UTIs. The EAC noted that these outcomes were based on evidence from poor quality studies which measured asymptomatic bacteriuria rather than symptomatic CAUTI.

5 Patient survey

NICE's public involvement programme circulated a survey in July 2021 to explore people's experience of using UroShield. A total of 15 responses were received. Results from responders were extracted and are summarised in Appendix D.

6 Ongoing research

The EAC identified 1 ongoing research project in the UK (CPMS ID 48290). This research project includes 3 individual studies: a controlled lab assessment, a before-and-after study, and a qualitative assessment on the use of UroShield. This research project is expected to be done between May to August 2021. There is also an ongoing RCT in Canada comparing UroShield with a sham device (NCT03785262). This study was estimated to be completed by February 2021 and no results were posted (clinicaltrials.gov record last updated in February 2020).

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7 Issues for consideration by the Committee

Clinical evidence

- The evidence base is limited in quality and quantity, with 8 relevant studies including 3 peer reviewed studies. The evidence is heterogenous, with different durations of catheter usage and outcomes. Is there enough quality evidence to support the use of UroShield in the NHS?
- The EAC's meta-analysis found a potential 73% reduction in bacterial infection with UroShield compared with comparators. Is bacteriuria an appropriate proxy measure for CAUTIs?
- The evidence suggests that using UroShield could reduce the risk of bacteriuria and symptomatic UTIs in people with long-term catheters. Is the evidence generalisable to the NHS population with long-term catheters?
- The EAC considered that the evidence for the benefit of UroShield in people with short-term catheters is limited and does not suggest any clinical benefit. Should patients with short-term catheters be considered for UroShield?
- Clinical experts suggested that the main benefit from UroShield is most likely to be seen in a community setting, in people with long-term catheters who are at high risk of CAUTI (including those with recurrent infections). Is the evidence sufficient to support the use of UroShield in these circumstances?
- Patients have reported positive effects of UroShield on physical health and quality of life. Many responders described the technology as life changing. Is there enough evidence to consider UroShield as an option for people whose quality of life is negatively affected by CAUTI?

Cost evidence

- The EAC's cost analysis suggested that the effectiveness of UroShield would be the driver for cost-savings, with increased effectiveness leading to cost saving in more populations. How certain are these cost savings given the quality of evidence?

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- UroShield was found to be cost saving in hospitals. The EAC base case showed the greatest cost savings to be in people in the ICU and people in hospital with long-term catheterisation. There was no clinical evidence on the use of UroShield in the ICU or in long-term catheterisation in hospitals. Does the evidence on UroShield generalise to these populations in the NHS?
- The use of UroShield in the community was only cost saving in people with recurrent UTI. UroShield is more likely to be cost saving as the risk of CAUTI increases. In what specific populations or settings in the community would the use of UroShield be cost saving or cost incurring?

8 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Poole RL, Pierce S, O'Connell S, et al. MT476 UroShield for preventing catheter-associated urinary tract infections: External Assessment Centre report, July 2021.

B Submissions from the following sponsors:

- NanoVibronix

C Related NICE guidance

- Healthcare-associated infections: prevention and control in primary and community care. NICE clinical guideline [CG139] (updated 2017). Available from https://www.nice.org.uk/guidance/cg139
- Healthcare-associated infections: prevention and control. NICE public health guideline [PH36] (2011). Available from https://www.nice.org.uk/guidance/ph36
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Markowitz S, Rosenblum J, Goldstein M et al. (2018) The effect of surface acoustic waves on bacterial load and preventing catheter-associated urinary tract infections (CAUTI) in long term indwelling catheters. Medical and Surgical Urology 7:4

Nagy K, Koves B, Tenke P (2011) The effectiveness of acoustic energy induced by UroShield device in the prevention of bacteriuria and the reduction of patients' complaints related to long-term indwelling urinary catheters. European Urology Supplements 10(2): 163-164

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NICE (2011) Healthcare-associated infections: prevention and control [PH36]

NICE (2017) Healthcare-associated infections: prevention and control in primary and community care [CG139]

NICE (2018a) Urinary tract infection (catheter-associated): antimicrobial prescribing [NG113]

Royal College of Nursing (2021) Catheter care: RCN guidance for health care professionals

Rosenblum J, Markowitz S, Goldstein M (2017) Surface acoustic waves prevent bacterial colonization in indwelling urinary catheters. European Urology Supplements 16(3)

Shenfeld O, Haris D (2010) The use of the UroShield device in patients with indwelling urinary catheters. Unpublished clinical trial report

Smith DRM, Pouwels KB, Hopkins S et al. (2019) Epidemiology and health-economic burden of urinary catheter-associated infection in English NHS hospitals: a probabilistic modelling study. The Journal of Hospital Infection 103(1): 44-54

Turan S, Bektas S, Yamak B et al. (2011) A new intervention for preventing urinary tract infections: Uroshield. [Turkish]. Gogus-Kalp-Damar Anestezi ve Yogun Bakim Dernegi Dergisi 17(4): 99-104. [English Language Translation provided by the company]

Zalut (2007). The effect of UroShield on pain and discomfort levels in patients released from the emergency room with urinary catheter due to urinary incontinence. Unpublished company report

Zillich S, Weber C, Ikinger U (2014) Replacement of antibiotic therapy by UroShield device in subjects with urinary catheter following radical prostatectomy.

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Jane Miles
Urology Nurse Specialist for Benign Disease, Frimley Health Foundation Trust

Ann Yates
Director of Continence Services, Cardiff and Vale University Health Board

Professor Marcus J Drake
Consultant Urologist, University of Bristol

Mustafa Ml Hilmy
Consultant Urological Surgeon, York Teaching Hospital

Dr Catriona Susan Anderson
Portfolio GP, Focus Medical Clinic

Sheilagh Reid
Consultant Urological Surgeon, Sheffield Teaching Hospital

Elaine Sutcliffe
Continence Team Leader, Hereford and Worcestershire Health and Care NHS Trust

Claire Fairbrother
Continence Nurse Prescribing Advisor, Northamptonshire Healthcare NHS Foundation Trust

For full details, please see the expert adviser questionnaire (EAQ) responses which are included in the committee pack.

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Appendix C: Comments from patient organisations

Advice and information were sought from patient and carer organisations.

A response was received from Bladder Health UK. Please see the response in the committee pack for full details.

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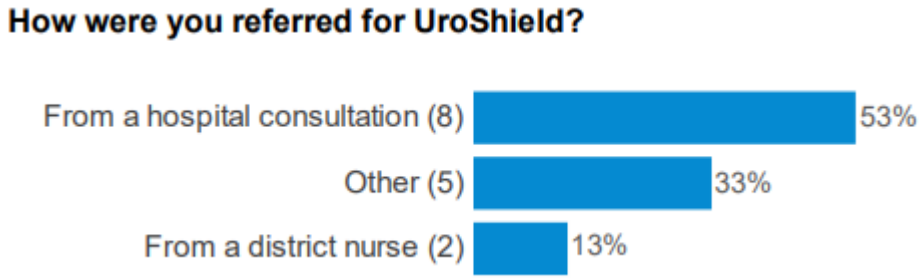
Appendix D: Patient survey

In July 2021, NICE's public involvement programme posted an online survey. Fifteen responses were received. All responders confirmed that they read the information sheet provided (which explains the purpose of the survey and how the information will be used) and consented to take part.

1.Responder demographics

Mean age of responders was 71.5 years, range 42–90 years (n=15). 53.3% of responders were male (n=8) and 46.7% were female (n=7). Eight responders were able to manage the device themselves (53.3%) and 7 responders had their carers help with using the device.

All responders had their catheters for long-term use (more than 28 days). Eight responders were referred for UroShield by hospital consultants. The others were referred by nurses including district nurses (n=2), a practice nurse (n=1), and continence nurse specialists (n=4).



2. UroShield for preventing the risk of catheter associated urinary tract infection

In addition to UroShield, 7 responders had other treatments for reducing the risk of CAUTI such as antibiotics (n=5) and the use of different catheters (n=3).

All responders reported a reduction in the number of episodes of CAUTI including 5 responders who did not have CAUTIs after using UroShield (1 responder had no CAUTI before using UroShield).

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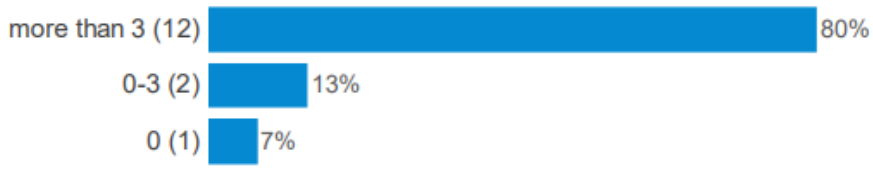
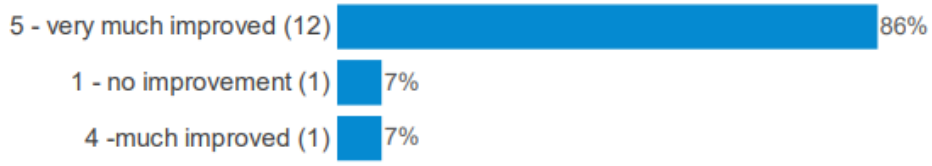
How many episodes of catheter-associated urinary tract infections have you had: (Before using UroShield)



How many episodes of catheter-associated urinary tract infections have you had: (After using UroShield)

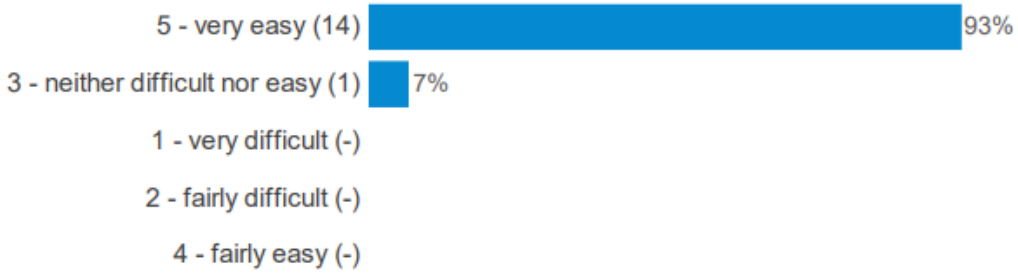
A total of 13 responders reported an improvement in symptoms (n=14 answered the question).

How would you rate the level of improvement in your catheter associated symptoms after using UroShield on a scale of 1-5? (1 is no improvement and 5 is the most improvement)



Most responders thought UroShield was easy to use.

How easy is UroShield to use on a scale of 1-5? (1 is the most difficult and 5 is the easiest)



Three responders reported the device stopped working including 2 having their devices replaced and 1 having battery life issues (did not last for a full day). One responder raised a concern that the use of Uroshield could be

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costly to the NHS because of the 30-day life cycle for an actuator which may result in more catheter changes than standard of care.

Positive effects

Most responders (14/15) described improvements to their physical health after using UroShield. One responder reported that they were midtrial of the device and felt it was too soon to comment. Benefits to physical health included less catheter blockages and changes, less bladder washouts, reduced discomfort and pain, and fewer infections. For some, this resulted in less need for antibiotics and fewer (or no) visits to A&E:

"Prior to using UroShield, my father had tens of catheter changes in one year due to infections and 'blockages'. These all had to be carried out in hospital. Post the fitting of UroShield, the next year he only had routine changes, a 100% betterment. Not only has it helped my father, but many of his hospital visits involved an ambulance & hospital admission due to the severity of his infection. This cost would be astronomical?" [Responder 7]

"*I feel better in myself for not being symptomatic on a monthly basis and not need to be constantly on antibiotics. It has helped to reduce pressure sores as I have not bypassed through night*." [Responder 9]

"*Since using the Uroshield this is the longest time in over four years I had not had an infection. The pain I have with my catheter improved after 2 weeks and has continued to be improved. I get a niggly pain and discomfort and I have tried various things including Morphine at one point. With Uroshield this has now all gone*." [Responder 11]

Most responders thought that their quality of life improved after using UroShield including improved mental health and wellbeing, reduced bypass, and improved sleep quality. Many responders described how UroShield had given them the freedom to leave the house and socialise again without worry:

"*I no longer need disposable sheets or pads. I have my dignity back! I have not had one infection since starting on the Uroshield*." [Responder 13]

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"Uroshield has improved my quality of life. Before the UroShield my suprapubic catheter was blocking a few times every day and stopped my going out as I would by-pass. I felt depressed. Since using the UroShield my catheter no longer blocks and I'm able to go out. I can't do without the UroShield it's been life changing for me." [Responder 15]

"My quality of life has improved dramatically as I no longer am prone to UTIs or catheter blockages. In the past when suffering a UTI I have had to rely totally on my wife for all my medical, physical and emotional needs as the result of a high temperature has a debilitating effect on me. My state of mind and wellbeing is so much better now that I am free of worrying about whether I am going to be struck down with yet another UTI." [Responder 14]

"It has improved my life so much physically and mentally every hospital admission would put me back further physically I would miss out spending time with friends and family when I was constantly having to stay home and turn them down in case of bypassing. It has helped me so much it scares me. The thought of this ever stopping" [Responder 8]

Negative effects

Half of the responders reported no negative effects of using UroShield. Comments on negative effects centred on the design of the device, with 5 responders commenting that the battery life could be longer. Other negative effects included inconvenience of the driver and discomfort from the attachment of the connection lead to the device. One participant reported getting an infection after the device was reattached incorrectly:

"*The only down sides to the unit are the battery life and it's not waterproof, I have designed a system that I use whilst showering to protect it, so I don't need to disconnect it every day. There was one occurrence when the nurse changed the actuator when my catheter was changed and put the clip on the wrong way, I did not notice and soon resulted in a UTI that month. It could be made slightly more clearer which is the correct way*." [Responder 9]

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"*Low battery light could come on sooner to allow more time to plug it in*." [Responder 12]

"Where the connection leads attach to the device can be a bit uncomfortable Disconnecting the driver when showering was difficult" [Responder 11]

"*Battery life would benefit from being longer. The unit is reasonably fragile and as such, this could be improved I am sure? We can see no other negatives*." [Responder 7]

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Appendix E: Decision problem from scope

	Scope
Population	People with indwelling urinary catheters across hospital and community settings.
Intervention	UroShield in addition to standard care
Comparator(s)	Standard care for preventing catheter associated urinary tract infection, including clinical observation such as documenting catheter blockages, reviewing the frequency of planned catheter changes, increasing fluid intake, and using prophylactic antibiotics when needed.
Outcomes	The outcome measures to consider include: • Incident rate of catheter associated urinary tract infection (CAUTI) • Rate of recurrence of CAUTI • Bacterial count in urine samples • Bacterial colonization levels (i.e. colony forming units) • Biofilm formation on the catheter lumen • Number of catheter changes • Number of catheter blockage • Antibiotics use • Number of outpatient visits • Number of hospital admissions including emergency admission to hospital • Reported pain and spasm • Ease of use (for patients and healthcare professionals) • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the different treatment options being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups	• People at high risk of developing CAUTI (for example, those with co-morbidities including diabetes or

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	underlying neurological conditions; those in clinical settings such critical care units). • People who have recurrent episodes of urinary tract infection (for example, 2 or more episodes in a 6-month period).	
Special considerations, including those related to equality	In adults, women are more likely to develop a catheter-associated urinary tract infection than men. Cerebrovascular disease and paraplegia are associated with an increasing likelihood of catheter-associated urinary tract infection. Sex and disability are protected characteristics under the Equality Act. Urinary tract infection is an important cause of morbidity and antibiotic use in older adults. Age is a protected characteristic under the Equality Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

UroShield for preventing catheter-associated urinary tract infections

1 Technology

1.1 Description of the technology

UroShield (NanoVibronix) is an ultrasound device designed to prevent bacterial colonisation and biofilm formation on indwelling urinary catheters. UroShield is intended to reduce the risk of catheter associated urinary tract infections (CAUTIs) in people with indwelling urinary catheters. UroShield is intended to be used as an add-on intervention to current standard care.

The technology works by generating low intensity 90kHZ ultrasonic surface acoustic waves which propagate throughout the catheter's entire length on both its inner and outer lumens. The company claims the acoustic waves interfere with the attachment of bacteria and formation of the biofilm. The company also claim the same acoustic waves reduce friction between the catheter and the patient’s internal tissues, thereby decreasing the pain, discomfort and spasm associated with indwelling urinary catheters.

UroShield includes 2 components:

- a driver (battery- or AC-powered portable unit), which provides the power (it is not water resistant), and
- a single-use actuator which is clipped onto the external portion of any indwelling urinary catheter and generates the ultrasonic waves.

UroShield can be used with catheters made of any material and size ranging from 12 to 22 French Gauge (FG). The UroShield can be powered by the mains or by a rechargeable battery, which can power the device for up to 6 hours when fully charged. The life expectancy of the driver is 2 years. The

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actuator is replaced every 30 days and should be disposed of when the catheter is replaced.

UroShield is not intended for use in children. It is not MRI compatible, and should be removed from the catheter before entering an MRI suite.

1.2 Relevant diseases and conditions

A urinary catheter is used to empty the bladder and collect urine in a drainage bag. Indwelling catheters remain in place for many days or weeks, and are held in position by an inflated balloon in the bladder. Some people may use catheters for their lifetime. Catheters are usually inserted by a doctor or nurse. An indwelling catheter can either be inserted through the urethra (indwelling urethral catheter) or through a small cut or incision in the lower part of abdomen (indwelling suprapubic catheter). Indwelling catheters may be used short term (usually up to around 14 days) or long term (weeks). Indwelling catheter prevalence varies in patient groups, settings and specialties. A study estimated that over 90,000 people in the UK had long-term catheters in the community (Gage et al. 2017). The study found most people were initially catheterised in hospital and that prevalence increased with age. Catheterisation was more common in people with neurological disease; and suprapubic catheterisation was more common in women.

Around half of people who have long-term catheters experience problems such as pain, tissue damage, decreased mobility and hospital attendances associated with blockage (Khan et al. 2007). People with indwelling urinary catheters are at increased risk of developing CAUTI. Nearly everyone with a catheter develops bacteria in their urine (bacteriuria) during the catheterisation period (Saint 2000). CAUTI is defined as the presence of symptoms or signs compatible with a urinary tract infection in people with a catheter with no other identified source of infection plus significant levels of bacteria in a catheter or a midstream urine specimen when the catheter has been removed within the previous 48 hours (NICE 2018).

Urinary tract infection is an important cause of morbidity and mortality in the healthcare setting, accounting for 19% of all hospital-acquired infections. Of

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these, it is estimated that between 43% and 56% are CAUTI (Loveday et al. 2014). However, there is limited data on CAUTIs in primary and community care settings. A local survey in England based on patient records during October 2014 reported that the prevalence of CAUTI in people with catheters in community settings was 8.5% (Getliffe and Newton, 2006).

CAUTI affects healthcare resources. People who have long-term catheters account for around 4% of a district nurse's caseload in the UK (Getliffe 1994). Daily management of people with catheters is often undertaken by community nurses, with input from general practitioners or secondary care for urinary tract infection or blockage that occurs out of hours. Health economic modelling estimates there are 52,085 CAUTI across NHS hospitals per year with direct hospital costs of £27.7 million (Smith et al 2019).

1.3 Current management

The NICE guideline on healthcare-associated infections states that the risk of blockages, encrustations and catheter-associated infections in long-term urinary catheters should be minimised through patient-specific regimens such as reviewing the frequency of planned catheter changes, increasing fluid intake, and documenting catheter blockages. Bladder instillations or washouts should not be used to prevent catheter-associated infections and catheters should be changed only when clinically necessary, or according to the manufacturer's recommendations. Prophylactic antibiotics should not be used routinely for catheter changes and only considered for patients who have a history of symptomatic urinary tract infection after catheter change, or who experience trauma during catheterisation.

NICE also published a public health guideline on healthcare-associated infections stating that hospital trusts regularly review evidence-based assessments of new technologies and other innovations to minimise harm from healthcare associated infections and antimicrobial resistance.

Healthcare professionals play a key role in caring for people with indwelling urinary catheters and reducing CAUTI. The doctor, specialist nurse or district nurse decides whether a person needs a catheter and how it should be

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managed, based on the individual's needs. The Royal College of Nursing published a practice guide for healthcare professionals, covering aspects of catheter care such as documentation, risk assessment and review of catheter care. In England, urinary catheter tools such as a catheter passport, catheter card and inpatient care plan have been used to allow healthcare professionals to document catheter care and share information between care services.

1.4 Regulatory status

UroShield is CE marked as a class IIa medical device.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Preventing catheter associated urinary tract infection (CAUTI), potentially leading to a reduction in the incidence of CAUTI.
- Improved quality of life in people with indwelling urinary catheters, with minimal disruption to patients' daily activities.
- Reducing catheter-related pain, spasm and discomfort.

The benefits to the healthcare system claimed by the company are:

- Reduction in costs and resources that could be associated with treating CAUTI such as unplanned hospital admissions, increased hospital length of stay and the use of antibiotics.
- Reduction in health service resource use that could be associated with the use of catheter such as avoiding catheter blockages, a reduction in the frequency of catheter changes and bladder washouts.
- Reducing the use of antibiotic prophylaxis.
- Ease of implementation; minimal changes in facilities or infrastructure needed if UroShield adopted in standard practice.

2 Decision problem

Population	People with indwelling urinary catheters across hospital and community settings.

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Intervention	UroShield in addition to standard care
Comparator(s)	Standard care for preventing catheter associated urinary tract infection, including clinical observation such as documenting catheter blockages, reviewing the frequency of planned catheter changes, increasing fluid intake, and using prophylactic antibiotics when needed.
Outcomes	The outcome measures to consider include: • Incident rate of catheter associated urinary tract infection (CAUTI) • Rate of recurrence of CAUTI • Bacterial count in urine samples • Bacterial colonization levels (i.e. colony forming units) • Biofilm formation on the catheter lumen • Number of catheter changes • Number of catheter blockage • Antibiotics use • Number of outpatient visits • Number of hospital admissions including emergency admission to hospital • Reported pain and spasm • Ease of use (for patients and healthcare professionals) • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the different treatment options being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• People at high risk of developing CAUIT (for example, those with co-morbidities including diabetes or underlying neurological conditions; those in clinical settings such critical care units). • People who have recurrent episodes of urinary tract infection (for example, 2 or more episodes in a 6-month period).
Special considerations, including those related to equality	In adults, women are more likely to develop a catheter-associated urinary tract infection than men. Cerebrovascular disease and paraplegia are associated with an increasing likelihood of catheter-associated urinary tract infection. Sex and disability are protected characteristics under the Equality Act. Urinary tract infection is an important cause of morbidity and antibiotic use in older adults. Age is a protected characteristic under the Equality Act.

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Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No

3 Related NICE guidance

Published

- Urinary tract infection in under 16s: diagnosis and management (2018) NICE clinical guideline CG 54.
- Urinary tract infection (catheter-associated): antimicrobial prescribing (2018) NICE NG113.
- Urinary tract infection (recurrent): antimicrobial prescribing (2018) NICE NG 112.
- Pyelonephritis (acute): antimicrobial prescribing (2018) NICE NG 111.
- Urinary tract infection (lower): antimicrobial prescribing (2018) NICE guideline NG 109.
- Healthcare-associated infections: prevention and control in primary and community care (2017) NICE clinical guideline CG139.
- Healthcare-associated infections: prevention and control (2011) NICE public health guideline PG 36.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Royal College of General Practitioners (RCGP)
- Royal College of Nursing (RCN)
- Royal College of Obstetricians and Gynaecologists

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- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Surgeons
- Association for Continence Advice
- Association of Physicians' Assistants
- Association of Healthcare Cleaning Professionals
- British Association of Urological Nurses
- British Association of Urological Surgeons
- British Infection Association
- British Nursing Association
- Community District Nurses Association
- Infection Prevention Society
- National Association of Primary Care
- Royal British Nurses' Association

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Action Bladder Cancer UK
- Bladder and Bowel Community
- Bladder and Bowel UK
- Bladder Health UK
- Brain and Spine Foundation (UK)
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- Multiple Sclerosis-UK
- Spinal Injuries Association
- Spinal Injuries Scotland (SIS)
- Urology User Group Coalition
- Urostomy Association
- WellBeing of Women

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- Women's Health Concern

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NICE National Institute for Health and Care Excellence

Adoption report: MT476 UroShield for preventing catheter-associated urinary tract infections

Summary

Adoption levers identified by contributors

- May benefit long-term catheter users when standard treatments are ineffective
- May reduce antibiotic use
- May decrease non-scheduled catheter changes due to blockages
- Non-invasive and simple to use
- Could be an additional option to prevent catheter associated urinary tract infection (CAUTI)

Adoption barriers identified by contributors

- Identifying additional funding for the technology
- 6-hour battery life may be restricting
- Identifying people suitable for its use may be challenging

1 Introduction

The adoption team has collated information from 7 healthcare professionals working within NHS organisations, 6 of whom have experience of using UroShield. It has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption and includes adoption considerations for the routine NHS use of the technology. It does not represent the opinion of NICE or MTAC.

UroShield has been available in the UK since 2018 and is currently used in 35 adults and 7 NHS organisations.

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2 Contributors

Details of contributing individuals are listed in the below table.

Site	Job title	Experience
1	Consultant urologist	Used with 10-20 people over past 3 years
2	Continence nurse prescribing advisor	Previous use within the trust for a trial with a small number of people with MS. Currently using for 1 person.
3	Clinical nurse specialist	Have started using with 2 people for a 12 week trial. Aim to recruit 10 people.
4	Consultant urological surgeon	No experience using UroShield.
5	Urology nurse specialist for benign disease	Used with 12 people over past 3 years
6	Retired gynaecologist	Lived experience of Uroshield for 2.5 years. Self-funded.
7	Clinical scientist	Have started using with 2 people for a 12 week trial. Aim to recruit 10 people.

3 Current practice in clinical area

There are 2 types of indwelling catheters discussed in this report, urethral and suprapubic. People have these catheters for a variety of reasons such as, neurological conditions, prostrate obstructions, or spinal injuries.

District nurses perform most catheter changes in the community. Some patients or their carers may be taught how to change their catheter. Those with complications may have them changed by specialists in secondary or tertiary care. Examples of complications can include:

- Hypersensitive bladders and painful catheter changes where analgesia such Entonox may be required.

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- Recurrent catheter blockages.
- Failed changes in the community.

Catheters are changed every 4-12 weeks, depending on the type used. Some people at risk of adverse symptoms from blockages such as autonomic dysreflexia for spinal cord injuries may have them changed as frequently as every 4-6 weeks.

Once an indwelling catheter is in situ, the management depends on local policy and the care pathway. According to contributors, measures to prevent catheter associated urinary tract infection (CAUTI) can include:

- Maintenance of a sterile closed uninterrupted drainage system.
- Prevention of catheter blockages. This could be by ensuring the person is kept hydrated and monitoring urine output.
- Regular catheter changes.
- Catheter maintenance using solutions such as saline or citric acid. Although a contributor said this was for preventing blockages and not for preventing CAUTI.
- Good bladder, bowel, and hand hygiene.
- Having a urinary catheter valve rather than a urinary drainage bag as the intermittent drainage flushes the catheter with urine. Urinary drainage bags are changed either daily or weekly depending on the type of bag.

If CAUTI is suspected the person or their carers either call their dedicated health professional (district nurse, GP, secondary or tertiary care) for advice and intervention or they may visit an A&E department. Intervention for symptomatic CAUTI is usually antibiotics, catheter change and, for a few people, an in-patient stay to manage symptoms of CAUTI.

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4 Use of UroShield in practice

A new catheter is used when people use the UroShield device for the first time. The actuators are then changed every 30 days by attaching to the existing catheter. When a catheter is changed, the company recommends using a new actuator. In practice, the health professional may coordinate the catheter change to coincide with changing the actuator. The company recommend the driver is replaced every 2 years. The contributor who personally uses UroShield has used the same actuator for 12 weeks to minimise cost and without any adverse reaction reported.

UroShield includes a driver and actuator and can be powered by mains using a charger or by an internal rechargeable battery. It has a 6 hour battery life and requires a 2-hour charge time when plugged into the mains. People can expose the actuator to water when having a bath or shower but not the driver. The driver is small and lightweight and can be attached using a lanyard or placed on the person's bed. It alarms if the battery charge is low or disconnected.

5 Reported benefits

The potential benefits of adopting UroShield, as reported to the adoption team by the healthcare professionals using the system or with expertise in this area are that it:

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- May benefit people with a long-term catheter when standard treatments are ineffective.
- May reduce use of antibiotics.
- May decrease non-scheduled catheter changes due to blockages.
- Non-invasive and simple to use.
- Could be an additional option to prevent CAUTI.

6 Insights from the NHS

Patient selection

Contributors agree most people with a long-term indwelling catheter will not need this technology. It is indicated for those with complications of long-term catheterisation such as CAUTI, bladder spasms or blockages and where standard treatment options are ineffective. One contributor specified he would use the following criteria:

- indwelling catheter for more than 3 months
- symptomatic urine sample verified CAUTI, with more than 4 occurrences per year*.

*This is different to the definition of recurrent urinary tract infection (UTI) in adults defined in Urinary tract infection (recurrent): antimicrobial prescribing which is defined as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months (European Association of Urology [EAU] guidelines on urological infections [2017]).

Another contributor reported they would only use it for people where they can ensure measures to prevent CAUTI are being followed, and this group may be difficult to identify.

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Clinician acceptance

The contributors clarified treatment for CAUTI usually includes antibiotics. Some people are becoming resistant to antibiotics and there are no alternative treatments to help them. Therefore, all contributors agreed the technology would be a useful alternative to prevent CAUTI and may also help decrease antibiotic use. Some contributors suggested that some clinicians may find it easier to treat with antibiotics than use a new technology.

One contributor reported approximately 30% of their unscheduled visits to patients in the community are due to catheter related issues (not all CAUTI) and that UroShield may help reduce this number.

Commissioning and procurement

None of the contributors have an identified budget for UroShield and stated this was the main barrier to adoption.

The manufacturer has offered UroShield for a trial period in most of the trusts interviewed. Following this trial some contributors have asked GPs to continue to fund the ongoing use of the device. A few GPs have refused to continue funding or are planning to submit an individual funding request (IFR) to their relevant clinical commissioning group (CCG).

One contributor suggested that in the absence of funding UroShield should be only used or recommended by specialists to ensure appropriate patient selection and measures to prevent CAUTI are being followed.

Training

All contributors agree the technology is simple to use. The company provide on-line and printed training materials for patients and their carers. One contributor suggested that people may need an additional appointment for training to understand where to place the actuator on the catheter, bathing instructions and charging the battery.

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Patient experience

All contributors said people have given positive feedback when using UroShield reporting that it is not invasive and simple to use. Furthermore, it prevents frequent episodes of CAUTI which some patients find painful and a burden.

Most contributors mentioned UroShield makes a humming sound. This can be useful to indicate the device is working but can be inconvenient when users want to be discrete. The contributor with lived experience of UroShield explained they were nervous to take a flight or sit near others in quiet places as they were embarrassed by the noise.

Maintenance

There have been incidences where untrained carers, unaware that UroShield needs plugging into the mains, have left it inactive after the battery has run out. This is not reported to be common but is a risk where multiple carers are involved in a person's care.

Some people do not like having a device attached to the mains even when they are in bed or sitting as they find it restrictive. The contributor who uses UroShield personally reported they always had to be aware of time to the next charge when planning their day to ensure access to a charging point. Most contributors agree UroShield would benefit from 2 battery packs or a longer battery life.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT476 UroShield for preventing catheter-associated urinary tract infections

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	NanoVibronix
Submission date	28th May 2021
Regulatory documents attached	CE Certificate Instructions for Use
Contains confidential information	No

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Contents

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1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with indwelling urinary catheters across hospital and community settings.	NA	Enter text.
Intervention	UroShield in addition to standard care	NA	Enter text.
Comparator(s)	Standard care for preventing catheter associated urinary tract infection, including clinical observation such as documenting catheter blockages, reviewing the frequency of planned catheter changes, increasing fluid intake, and using prophylactic antibiotics when needed.	NA	Enter text.
Outcomes	Bacterial count in urine samples • Bacterial colonisation levels (i.e. colony forming units) • Number of catheter changes • Number of catheter blockage • Antibiotics use • Number of outpatient visits • Number of hospital admissions including emergency admission to hospital: • Ease of use (for patients and healthcare professionals),	NA	Enter text.

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	including training requirements • Device acceptability and patient satisfaction • Health-related quality of life • Device-related adverse events		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	NA	Enter text.
Subgroups to be considered	• People at high risk of developing catheter associated urinary tract infection (for example, those with co-morbidities including diabetes or underlying neurological conditions). • People who have recurrent episodes of urinary tract infection (for example, 2 or more episodes in a 6-month period). • People with short-term indwelling catheter use (for	NA	Enter text.

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	example,14 days or less) and those with long term catheter use. • People in different clinical settings (for example, those in hospital and those in community settings).		
Special considerations, including issues related to equality	In adults, women are more likely to develop a catheter-associated urinary tract infection than men. Cerebrovascular disease and paraplegia are associated with an increasing likelihood of catheter-associated urinary tract infection. Sex and disability are protected characteristics under the Equality Act. Urinary tract infection is an important cause of morbidity and antibiotic use in older adults. Age is protected characteristics under the Equality Act.	NA	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	UroShield
Approved name	UroShield
CE mark class and date of authorisation	IIa MDD as amended by Directive 2007/47/EC

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Version(s)	Launched	Features
39.05	7 November 2019	1. Firmware improvement self-regulation, hardware product upgrade following commercial feedback 2. Implementation of EMC IEC 60601-1-2 rev. 4.0 standard
37.05	30 April 2019	Improvement UroShield Driver Functionality
35.05	5 February 2018	Changing screen saver in the Working Mode
33.05	7 December 2015	Improvement of self-regulation function, repair software bugs during USB connection
32.05	6 May 2015	Additional function to working mode – battery charging during driver operation. Functionality upgrade to firmware rev.32.05 from base driver FD – 14A firmware rev.31

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What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Preventing catheter associated urinary tract infection (CAUTI), potentially leading to a reduction in the incidence of CAUTI.	Markowitz et al, 2018; Zillich et al, 2014; Nagy et al, 2011; Ikinger et al, 2007; Da Silva 2021; Shenfeld and Haris, 2010.	All studies showed either a reduction in bacteria/CFU or bacteriuria which in turn results in a reduction in UTI and CAUTI.
Improved quality of life in people with indwelling urinary catheters with minimal disruption to patients' daily activities	Da Silva 2021; Zalut	Da Silva included qualitative feedback and analysis which indicated that overall patient wellbeing was improved with UroShield. Zalut reported an overall increase in wellbeing score from 3.3 to 7 over 4 days with UroShield
Reducing catheter-related pain, spasm and discomfort.	Nagy et al, 2011; Zalut; Da Silva 2021; Shenfeld and Haris, 2010	All studies reported a reduction in pain, spasm and discomfort scores.
System benefits		
Reducing the use of antibiotic prophylaxis	Zillich et al 2014	Zillich demonstrated improved outcomes for patients with just UroShield compared to control group treated with additional antibiotics (trimethoprim).
Ease of implementation; minimal changes in facilities or infrastructure needed if UroShield adopted in standard practice	Da Silva 2021; Shenfeld and Haris, 2010 Zalut	User feedback on ease of use and overall tolerability. Zalut reported that UroShield could be used in the home care setting.
Cost benefits		
Reduction in costs and resources that could be associated with treating CAUTI such as	Shenfeld and Haris, 2010 Da Silva 2021	Shenfeld and Haris reported that the overall pain

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additional clinician visits, hospital admissions and the use of antibiotics		medication use was reduced in the UroShield group. Da Silva reported a significant reduction in antibiotic use over 12 weeks in NHS patients.
Reduction in health service resource use that could be associated with the use of catheter such as avoiding catheter blockages, a reduction in the frequency of catheter changes and bladder washouts.	Da Silva 2021	Da Silva reported a significant reduction in catheter changes but not bladder washouts over 12 weeks in NHS patients
Sustainability benefits		
Reduced number of catheters due to increased length of time between changes	Da Silva, 2021	Number of catheter changes reduced from a baseline value of 2.91 to 0.32 (p=0.001) after 12 weeks of UroShield use.
Enter text.	Enter text.	Enter text.

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Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

UroShield is a disposable ultrasound device designed to reduce the risk of catheter-associated urinary tract infection (CAUTI) and improve the quality of life for patients. Urinary catheters readily acquire biofilms after insertion; and the longer the catheter remains in place, the greater is the tendency for the formation of biofilms, resulting in urinary tract infections. The device reduces bacterial colonisation and biofilm formation on indwelling urinary catheters.

The initial step in biofilm formation is the adhesion or attachment of planktonic bacteria to the catheter surface. It is thought that the bacteria use touch sensors to attach to a solid surface. This occurs within a few hours after urinary catheter placement. After attachment, the bacteria begin to interlock, a process known as docking. The bacteria then secrete an extra-cellular polymeric matrix (ECM), which allows them to survive and proliferate. The complex of the bacteria and ECM, now adherent to the catheter surface, is known as biofilm. The established biofilm is highly resistant to antibiotics and to the body's immune system.
The technology works by generating and propagating low frequency low intensity ultrasonic surface acoustic waves throughout the catheter, which interferes with the attachment of bacteria. The waves travel in longitudinal direction, parallel to the propagation of the wave and across the catheter surface, which in-turn triggers horizontal particle displacement. This results in transversal compression waves which travel over the tissue and fluid surrounding the catheter, thereby ensuring all surfaces, including the catheter and adjacent biological material are affected by the ultrasound. The waves are transmitted directly onto the indwelling catheters at frequencies of 90 kHz and propagate throughout the catheter's entire length on both its inner and outer lumens.

The action of the ultrasonic waves on the surfaces of the catheter interfere with the attachment of bacteria, prevent infections developing, reduce catheter encrustation and blockages and decrease or eliminate the need for antibiotics, reducing risk and improving patient outcomes. This in turn reduces the costs associated with indwelling catheter complications that may lead to increased medication and extended hospital stays.
UroShield can be used with catheters made of any material and sized 12, 14, 16, 18, 20, or 22 French Gauge (FG).

UroShield includes 2 components: a driver (battery- or AC-powered portable unit), which provides the power, and a single-use actuator which is clipped onto the external portion of any indwelling urinary catheter and generates the ultrasonic waves. The actuator component of UroShield can be used for up to 30 days before needing to be replaced. If a catheter is changed within the 30-day lifespan of an existing actuator use, the actuator can be removed and attached to the new catheter for the remaining days. Following training, patients or carers can change the actuator component of UroShield themselves. UroShield is not MRI compatible, and should be removed from the catheter before entering an MRI suite. UroShield should not be used for treating an active urinary infection.

The innovative aspects are that the device uses surface acoustic wave technology to prevent bacteria attaching to the surface of catheters. The acoustic waves create an acoustic envelope on the surfaces of the catheter, decreasing friction between the urethra and the urinary catheter and therefore, as had been shown in animal studies, reduces tissue trauma caused by the catheter. The tissue in contact with the catheter remains healthier as a result of the application of acoustic lubrication on the catheter surfaces, decreasing pain, spasm and discomfort associated with catheters. UroShield may have the potential to eliminate or reduce antibiotic use, by preventing infection completely or if a urinary tract infections occurs, reducing the patient's dose or shortening

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their treatment course. By minimising the exposure of bacteria to antibiotics, the technology has the potential to help reduce antibiotic resistance.

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Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

The use of UroShield helps to reduce catheter blockages and infections, resulting in fewer catheter changes being necessary and fewer unscheduled patient visits by community clinicians.

General studies of CAUTI demonstrate a relatively high use of antibiotics for this patient population. A reduction in infections would result in a reduction in antibiotic prescribing and reduce the risk of antimicrobial resistance in this patient group.

It is difficult to infer overall infection risk in community catheter patients, particularly in CAUTI, as relative use of primary vs secondary care services is unknown. However, although these figures may not be representative, crude comparison with the present results suggests that 10% of community catheter patients are hospitalised annually with CAUTI and 5% with CABSI (Smith et al, 2019)

An NHS study on long term catheter management in the community reported that unplanned catheter related events occur regularly with 43% of participants accessing out of hours services and 15% accessing A&E over the 12 month period. Moreover, one third of District Nurse visits were outside of routine scheduled care and some hospitalisations may be avoidable (Gage et al, 2017)

These unplanned events due to CAUTI create additional demands on patients and clinicians which impact the environment through the necessity for additional clinician, patient and carer time and transport expenditure.

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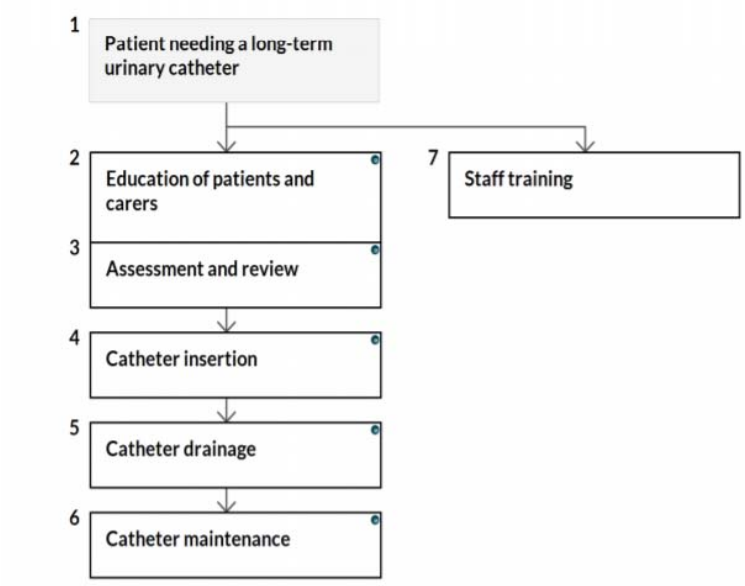
3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

Patients at high risk of developing CAUTI would be considered for UroShield Treatment under the current NICE care pathway for "Prevention and control of healthcare-associated infections in primary and community care – Patient needing a long-term urinary catheter". (Fig 3.1)
UroShield would be an appropriate consideration under point 3 of this pathway, "assessment and review". Patients assessed and identified to be at high risk of CAUTI, "UroShield Treatment". To support the existing model we have provided a supplementary pathway to show the pathway including the decision to prescribe UroShield Treatment. (Fig 3.2)
High risk patients could be identified using the following criteria; Gender, History of urinary tract problems (e.g., enlarged prostate or urologic surgery), Neurologic conditions (e.g., spinal cord injury) causing neurogenic bladder problems, Previous UTIs, Previous and/or current abnormal voiding patterns, Current catheter history, Incontinence, Comorbid conditions such as diabetes, Immunosuppression.

Long term catheterisation is defined by NICE as greater than 28 days. There is presently no NICE pathway for secondary care, nor for short term catheterisation where patients have been identified as potentially at high risk of CAUTI. As UTIs are a leading cause of HCAI and gram negative bloodstream infections, we propose that this population is considered and a NICE care pathway developed to include this patient group. A pathway has been proposed below which includes all at risk patients in secondary care. (Fig 3.3) UroShield Treatment would be an appropriate consideration under point 3 of this pathway, "Assessment and Review". Patients assessed and identified to be at high risk of CAUTI, and who are expected to be catheterised for greater than 48hours should be considered for UroShield Treatment. To support the existing model we have provided a supplementary pathway to show the UroShield Treatment decision. (Fig 3.2)
https://www.nice.org.uk/guidance/cg139/ifp/chapter/long-term-use-of-urinary-catheters

FIG 3.1 Prevention and control of healthcare-associated infections in primary and community care – Patient needing a long-term urinary catheter.



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https://pathways.nice.org.uk/pathways/prevention-and-control-of-healthcare-associated-infections#path=view%3A/pathways/prevention-and-control-of-healthcare-associated-infections/preventing-infection-related-to-long-term-urinary-catheters.xml&content=view-index

FIG 3.2 Supporting pathway

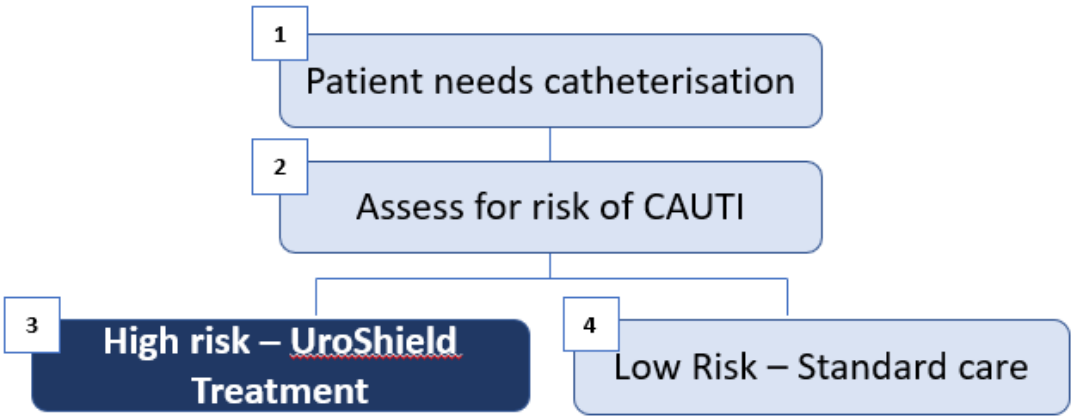
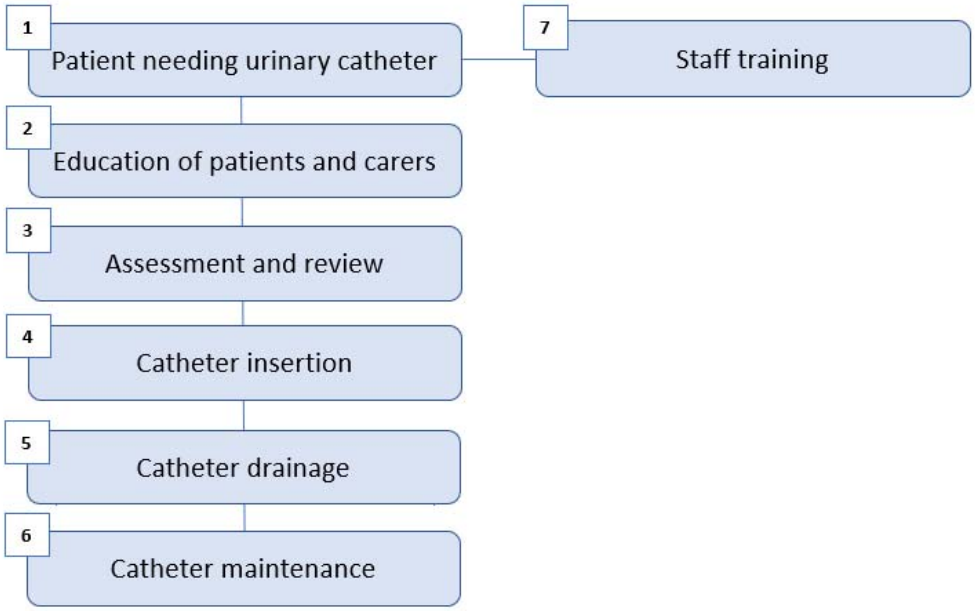


FIG 3.3 Suggested pathway prevention and control of healthcare-associated infections in secondary care – Patient needing a urinary catheter.



Patients with recurring CAUTI would be considered for UroShield Treatment under the existing NICE pathway for "Urinary tract infections in people aged 16 years and over – With a catheter."

(Fig 3.4) UroShield Treatment would be an appropriate consideration under point 4 of this pathway, "when to refer to hospital or seek specialist advice", patients would be assessed for UroShield suitability and if they meet the criteria UroShield Treatment would be prescribed. Please see supporting pathway (Fig 3.5) which includes the proposed use of UroShield.

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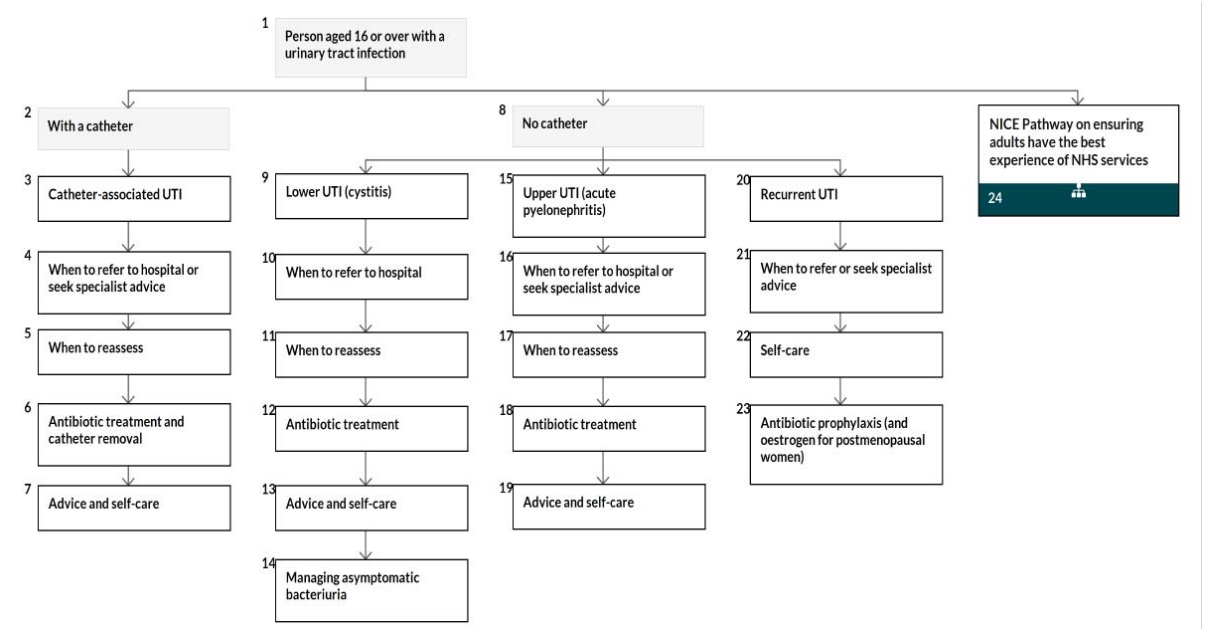
FIG 3.4 Urinary tract infections in people aged 16 years and over – With a catheter.



https://pathways.nice.org.uk/pathways/urinary-tract-infections#path=view%3A/pathways/urinary-tract-infections/urinary-tract-infections-in-people-aged-16-years-and-over.xml&content=view-node%3Anodes-when-to-refer-to-hospital-or-seek-specialist-advice-catheter

FIG 3.5 Supporting pathway

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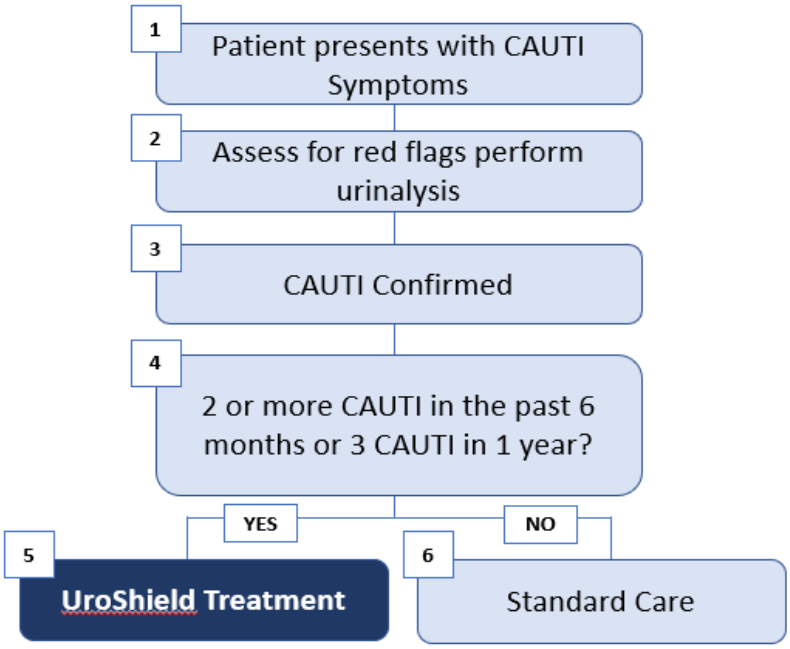

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Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The UroShield device requires a minimum of training effort.

It is presently attached to the exterior part of the catheter by the clinicians who insert the catheters: doctors, specifically trained nurses (urology nurse specialists), district/community nurses, continence care nurses.

In many cases, the patients and carers can manage the device themselves following training.

In addition to the Instructions for Use and Quick Start Guide, an online video is available.

Where health care organisations are using for the first time, training is made available through personal visits or scheduled online training sessions.

When required, further support is available for clinicians, patients and carers through a specialist nurse advisor and helpdesk team.

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4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		601
Number of studies identified as being relevant to the decision problem.		7
Of the relevant studies identified:	Number of published studies (included in table 1).	1
	Number of abstracts (included in table 2).	4
	Number of ongoing studies (included in table 3).	3

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

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Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Company website	Markowitz et al, 2018. USA	Double-blind RCT	Adults who were nursing home residents with long-term (>1year) indwelling urinary catheter	UroShield device, n=29 Patients received the UroShield device for the first 30 days and then received standard care for the remaining 60 days (2 catheter changes).	Sham device , n=26 Patients followed the same treatment regimen	Microbial counts (CFU) in urine and on catheter Infection requiring antimicrobial therapy

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Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Company website	Zillich et al, 2014 Germany	Prospective randomised 2 arm study	Patients with urinary catheter after radical prostatectomy	UroShield + Ceftriaxone, n=20	ceftriaxone and Trimethoprim, n=20	Catheter days Bacteriuria
Embase	Nagy et al, 2011 Hungary	Prospective non-randomised comparative study	Patients with long term urinary catheter 2 withdrawals due to adverse events in each group	UroShield, n=14	Standard care, n=13 (urinary catheter only)	Microbial counts (CFU) in urine Pain score (1-10) Adverse events/complaints SEM for biofilm assessment
Company	Ikinger et al, 2007 Germany	Double blind sham controlled RCT	Patients with urologic cancers	UroShield active, n=11	UroShield sham, n=11	Bacteriuria SEM for biofilm assessment Safety
Company website	Zalut et al, 2007 Israel	Open label treatment study	Patients released from the ER with a urinary catheter	UroShield, n=10	None	Pain, itching, burning, spasm, well being

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Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Company	Da Silva, 2021 UK Submitted Journal of Urology	Prospective open label treatment study with before and after outcomes	Patient with catheters	UroShield, n=29	Patients were compared to their own baseline i.e. standard care prior to using UroShield	UTI rates Antibiotic use Blockages Unplanned changes Bladder washouts Pain
Company	Shenfeld and Haris, 2010 Israel	Open label comparative RCT	Patients with in-dwelling catheter Hospital setting	UroShield, n=27	Standard care, n=13 (urinary catheter only)	Pain, Discomfort and Spasm levels Presence of clinically significant UTI Presence of bacteriuria Antibiotic and pain medication treatment The following outcomes were planned but not reported: Tissue damage Catheter changes Biofilm
NIHR CRN Portfolio Search	Wilks et al, ongoing clinical trial (currently recruiting) NBIC and University of Southampton sponsors 2020	Open label interventional study with before and after outcomes Lab study and Patient study Quantitive and Qualitative	Patients with long term indwelling catheters	UroShield n = 30	Patients will be compared to their own baseline i.e. standard care prior to using UroShield	

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Table 4 Results of all relevant studies (from tables 1, 2 and 3)

<table>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td>Markowitz et al, 2018</td><td>Patients from a skilled nursing facility and who required long term catheterisation were recruited into the study.
Patients received either the UroShield or sham device for the first 30 days and then received standard care for the remaining 60 days (2 catheter changes).
Bacteriuria
<table>
<tr><th>Mean CFU</th><th>Baseline</th><th>30 days</th><th>60 days</th><th>90 days</th></tr>
<tr><td>Sham, n=25</td><td>>100K</td><td>>100K</td><td>>100K</td><td>>100K</td></tr>
<tr><td>UroShield, n=29</td><td>>100K</td><td>-87.2K (t (53) 18.1, p<0.001)</td><td>-87.5K (t (53) 18.1, p<0.001)</td><td>-79.3K (t (53) 12.4, p<0.001)</td></tr>
</table>
In the UroShield group after the 30 days of treatment, there was no statistically significant increase in CFU between 30-60 days (t (28)=1. p= .326) or between 60-90 days (t(28)=1.7 p= 0.09).

Infection
<table>
<tr><th>Infections</th><th>Baseline</th><th>30 days</th><th>90 days</th></tr>
<tr><td>Sham</td><td>0</td><td>7</td><td>14</td></tr>
<tr><td>UroShield</td><td>0</td><td>0</td><td>3 (p=0.001)</td></tr>
</table></td><td>CFU counts greater than 100,000 are considered clinically relevant and sufficient to initiate antimicrobial therapy if required particularly in symptomatic patients but prescribing is dependent upon clinical judgement.
The UroShield device was extremely effective as a bactericidal agent. The device was able to reduce the CFU count from 100,000 to 10,000 CFU or less in 25 of the 29 patients within the treatment group (p value of <0.001 compared to control).</td></tr>
<tr><td>Zillich et al, 2014</td><td>Patients who had undergone radical prostatectomy were recruited to the study.
Group 1 - Post operative single dose of Ceftriaxone 2g + Active UroShield</td><td>Bacteriuria determined from bacterial counts but the report is unclear on how bacteriuria is defined.
Outcomes were improved in UroShield patients who did not receive additional prophylactic antibiotics (trimethoprim).</td></tr>
</table>

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<table>
<tr><td></td><td>Group 2 - Post operative dose of Ceftriaxone 2g on Day 1-3 + trimethoprim 2x200mg per day until the end of the study.<table><tr><th></th><th>UroShield, n=20</th><th>Control, n=20</th></tr><tr><td>Catheter days</td><td>8.4 days (range 7-12)</td><td>8.3 (range 7-10)</td></tr><tr><td>Cases of bacteriuria</td><td>1 / 20 (5%)</td><td>4 / 20 (20%)</td></tr></table></td><td>UroShield is superior to daily antibiotic treatment in preventing bacteriuria and therefore UTIs in radical prostatectomy.</td></tr>
<tr><td>Nagy et al, 2011</td><td>Patients required long-term catheterisation were recruited to the study. The UroShield in place for 8 weeks.<table><tr><th></th><th>UroShield, n=14</th><th>Control, n=13</th></tr><tr><td>Mean age</td><td>75 (49-82)</td><td>76.7 (56-89)</td></tr><tr><td>Female: male</td><td>3:11</td><td>3:10</td></tr><tr><td>Withdrawals</td><td>2</td><td>2</td></tr><tr><td>Prostate cancer</td><td>7</td><td>6</td></tr><tr><td>BPH</td><td>3</td><td>4</td></tr><tr><td>Urinary incontinence</td><td>3</td><td>2</td></tr><tr><td>Vesicoureteral reflux</td><td>1</td><td>1</td></tr></table>Bacteriuria<table><tr><th></th><th>UroShield</th><th>Control</th></tr><tr><td>Significant Bacteriuria (CFU)</td><td>4 / 12 (33%)</td><td>9/11 (81%)</td></tr><tr><td>Aeruginosa biofilm</td><td>0/12</td><td>3/11 (27%)</td></tr><tr><td>E.coli biofilm</td><td>1/12 (8%)</td><td>2/11 (18%)</td></tr><tr><td>Enterococcus face. Biofilm</td><td>1/12 (8%)</td><td>2/11 (18%)</td></tr><tr><td>Proteus mirabilis biofilm</td><td>1/12 (8%)</td><td>1/11 (9%)</td></tr></table></td><td>Significant bacteriuria is defined as greater than 10^5 CFU/ml of one organism.
Withdrawals due to adverse events – see Section 6.
Long-term (8 weeks) use of UroShield can reduce the rate of significant catheter-associated bacteriuria and can reduce patient reported catheter-related complaints.</td></tr>
</table>

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Klebsiella Pn biofilm	1/12 (8%)	1/11 (9%)

No symptomatic UTI were reported in either group.

Pain Scores were determined by VAS scale (1-10 scale) and reported as catheter-related complaints in both all patients and those who had at least moderate symptoms (score ≥ 3)

All patients	**0**	**2**	**4**	**6**	**8**
Control	2.1	1.9	2.1	2.7	3.4
UroShield	2.6	1.5	1.5	1.2	1
Moderate Symptoms	**0**	**2**	**4**	**6**	**8**
Control	3.7	4.1	3.9	4.7	5.7
UroShield	4.2	3.0	2.3	1.9	1.8

SEM analysis of biofilm formation

	UroShield	**Control**
Biofilm formation	1 / 12 (8%)	9 /11 (81%)

Ikinger et al, 2007

Patients with urologic cancers were recruited to the study

Reason	**Control group (n)**	**Active Group (n)**
Prostate cancer	9	7
Kidney cancer	1	3
Kidney cyst	0	1
Tumour of penis	1	0
Total	11	11

Biofilm formation (SEM analysis)

No specific data reported for the bacteriuria outcomes.

The UroShield device prevented biofilm formation on urinary catheters.

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<table>
<tr>
<td></td>
<td>
<table>
<tr><td></td><td>Control (n)</td><td>Active (n)</td></tr>
<tr><td>Biofilm</td><td>7</td><td>0 (zero)</td></tr>
</table>

Bacteriuria
No statistical significant difference between the 2 groups
</td>
<td></td>
</tr>
<tr>
<td>Zalut et al 2007</td>
<td>Patients who were released from the ER with a urinary catheter were recruited to the study.
Average age of patients was 64.5 (27-82)
Pain and discomfort levels were recorded daily for 4 days using a questionnaire (scale 1-10)
<table>
<tr><td></td><td>Day 1</td><td>Day 4</td></tr>
<tr><td>Pain</td><td>6.1</td><td>1.8</td></tr>
<tr><td>Itching</td><td>2.6</td><td>0.4</td></tr>
<tr><td>Burning</td><td>3.7</td><td>0.2</td></tr>
<tr><td>Spasm</td><td>3.7</td><td>1.0</td></tr>
<tr><td>Wellbeing</td><td>3.3</td><td>7.0</td></tr>
</table>
</td>
<td>The study demonstrated that UroShield is effective in subjects that suffer from pain and discomfort due to urinary catheters. The ability to use it in the home care setting can improve the subject's tolerance to urinary catheters and improves catheter related injuries.</td>
</tr>
<tr>
<td>Da Silva, 2021</td>
<td>Patients with urinary catheters, were recruited to the study with 23/29 completing the study which ran for 12 weeks
Time of use/wear – most wore UroShield for 93% of the time with none wearing it less than 67% of the time
<table>
<tr><td></td><td>N (base/end)</td><td>Baseline Mean (SD)</td><td>End of study Mean (SD)</td></tr>
<tr><td>UTI</td><td>21/22</td><td>3.24 (±3.42)</td><td>0.5 (±0.91), p=0.001</td></tr>
<tr><td>Antibiotic Use</td><td>22/22</td><td>2.05 (±2.33)</td><td>0.77 (±1.11), p=0.009</td></tr>
</table>
</td>
<td>Real world non-comparative data gathered between Sept 2019 -October 2020. Initial recruitment of 29 patients (84% power) that was reduced to 23 participants (73%) by the end of the study.
The data was not normally distributed and Wilcoxon signed ranks non-parametric tests were used to determine significant changes between baseline and the last 3 weeks of the trial.
Thematic analysis reported a positive narrative feedback on the device use grouped into 2 themes.
The findings suggest significant improvement across all outcomes except bladder washouts with the UroShield. Overall well-being was also improved.</td>
</tr>
</table>

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	Blockages	22/22	2.59 (±3.75)	0.36 (±0.9), p=0.006
	Catheter changes	22/22	2.91 (±3.57)	0.32 (±0.48), p=0.001
	Bladder washouts	17/17	2.71 (±6.01)	0.65 (±1.69), p=0.104
	Pain	21/20	3.30 (±2.23)	2.6 (±1.86), p=0.017

Patient feedback

No effect on sleep

50% felt happier about their catheter, no-one reported feeling worse

9/22 reported being able to do more things with 4 people not reporting changes

All patients responded that it was simple, easy to use and they felt comfortable using it and that they felt they benefited from using the UroShield.

Thematic analysis (narrative)

Positive outcome themes: changes to well-being and device design. This theme was represented by the largest volume of comments from patients.

Negative outcomes themes: caused by patients other conditions and minor inconvenience

In summary, there were also improvements to the participants over-all well-being including reduced levels of worry, improved ability to socialise and increased levels of independence.

Shenfeld and Haris, 2010	**Patients** in hospital with an indwelling catheter (more than 24 hours) were recruited into the study and treated with the device for 13 days.	The original study was approved for 210 patients but due to funding issues, it was decided that the trial should close at 40 patients. There were no protocol violations and only minor

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Demographics

	Control (SD, ±range)	UroShield (SD, ±range)
n	13	27
Age	52 ±14.45 (20-72)	50±18.70 (20-77)
Gender (F:M)	3 : 10	3 : 24
BMI	26.28±4.73 (19.03-32.02)	26.34±4.39 (36.67 18.25)
Heart rate	82.76±12.17 (97- 58)	75.33±14.71 (104- 54)
BP Systolic	136.61±15.23 (160-107)	123.28±18.69 (180-100)
BP Diastolic	79.07±11.67 107-64)	74±11.31 (91-55)

Catheter size

Control 17±3.94 (24-14)

UroShield 16±3.18 (24-14)

Pain and discomfort scores (mean ± SD)

Parameter	Control	UroShield
Pain	3.2 ±2.7	2.2±2.7, p=0.02 (31% reduction)
Discomfort	4.0 ±3.3	2.8 ±3.0, p=0.01 (30% reduction)
Spasm	3.62 ±3.2	2.53 ±2.7, p=0.01 (32% reduction)

Bacteriuria – % positive bacteriuria levels

deviations to enable the UroShield to be used on 24Fr catheters, up from 22FR as detailed in the protocol.

The study groups are similar in terms of physical and medical parameters including reasons for hospitalisations, catheter size and type and number of lumens.
Student's t-test (paired samples, two tail, unequal variance) was performed to determine the difference between pain, spasm and discomfort levels for active group and control group patients. Fishers exact test was used for the bacteriuria data.

The pain, discomfort and spasm scores are reported by each treatment day with the average scores being reported here. It should be noted that the pain medication was given for any condition, not just those related to catheter.

The incidence of bacteriuria was also reduced in UroShield patients at day 3 only. The data from the other days was not considered robust enough for analysis.

The patients reported the device was comfortable and easy to use. Adverse events are reported in Section 6.

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Measurement Day	**Control**	**UroShield**
Day 0	20% (n=15)	7.1% (n=28), p=0.32
Day 3	10% (n=10)	5.3% (n=19), p=0.33
Day 6	0% (zero) (n=4)	50% (n=4), p=0.42
Day 9	0% (zero) (n=2)	0% (zero) (n=2)
Day 12	0% (zero) (n=1)	No data

The number of subjects from day 6 and onward is insufficient for estimating the rate of bacteriuria.

Pain and Medication Use

Parameter	**Control**	**UroShield**
Use of pain/spasm medication	11/13 (85%)	17/27 (63%)
Medication strength	3.7	3.3

Tolerability

All patients reported that the device was comfortable and easy to use with no tolerability issues reported.

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5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Markowitz 2018	
How are the findings relevant to the decision problem?	The RCT was undertaken in a relevant patient population of patients with long-term indwelling catheters in a community setting and included relevant outcomes as detailed in the decision problem. The comparator device was a sham device in addition to standard care. The results show a significant reduction in CFU after 30 days of use that persists for up to 60 days. Similarly, the number of infections that required antibiotic treatment were also reduced which could also impact on healthcare costs through reduced antibiotic prescriptions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence supports the claim of preventing catheter associated urinary tract infection (CAUTI), potentially leading to a reduction in the incidence of CAUTI. The results also support the cost savings from a reduction in both CAUTI and associated therapeutic antibiotic usage.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The published paper only contains limited information so the study protocol and report have been provided separately to demonstrate how the study was undertaken.
How was the study funded?	This study was funded by NanoVibronix Inc.

Zillich 2014	
How are the findings relevant to the decision problem?	The RCT was undertaken in the relevant patient population of patients requiring short term catheterisation post-prostatectomy surgery and included relevant outcomes as detailed in the decision problem. The comparator device was standard care with additional antibiotics. The results show a significant reduction in catheter days and incidence of bacteriuria with UroShield and without the need for prophylactic antibiotics. This study indicates that even in short-term catheterisation, the number of catheter days can be reduced as can the incidence of bacteriuria

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Does this evidence support any of the claimed benefits for the technology? If so, which?	This study supports the claim to prevent CAUTI though a reduction in bacteriuria. The reduction in catheter days would support the claims for reducing the resource usage associated with CAUTI. There was also a reported reduction in antibiotic prophylaxis and analgesics.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The data is published on the company website and has not been peer-reviewed or published in a scientific journal. The data only contains limited information regarding the study protocol, patient demographics and how the study was undertaken. The study data is not presented in a clear and detailed format. The patients did not have long term indwelling catheter usage as the catheter was used post-surgery.
How was the study funded?	NanoVibronix provided the devices only and did not directly fund the study.

Nagy 2011	
How are the findings relevant to the decision problem?	This comparative study was undertaken in the relevant patient population of patients with long-term indwelling catheters for a variety of conditions and included relevant outcomes as detailed in the decision problem. The comparator device was standard catheter care. The results show a significant reduction in bacteriuria and pain scores, particularly in those patients experiencing moderate pain.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence presented in this poster supports the benefits of reduced CAUTI through reduced bacteriuria and reduced catheter-related pain. Any reduction in bacteriuria/CAUTI is expected to translate to a reduction in costs for the NHS from both a reduction in the need for NHS resources as well as antibiotic use.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The data is published as a conference abstract/poster presentation and has not been peer-reviewed. The data only contains limited information regarding the study protocol, patient demographics and how the study was undertaken.

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How was the study funded?	Study was funded by the Jahn Ferenc South-Pest Hospital, Dept. of Urology, Budapest, Hungary. NanoVibronix provided the devices only and did not directly fund the study.

Ikinger 2007	
How are the findings relevant to the decision problem?	This RCT was conducted in a relevant population consisting of patients requiring short-term catheterisation as detailed in the decision problem. The comparator was a sham device and the study showed a reduction in biofilm formation in the active group. The poster reports that no statistical significance was found with respect to bacteriuria between the active and sham groups
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence supports the claim to reduce CAUTI through the reduction in bacterial colonisation and biofilm formation on urinary catheters. Any reduction in CAUTI is expected to translate to a reduction in costs for the NHS from both a reduction in the need for NHS resources as well as therapeutic antibiotic use.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The data is published as a conference abstract/poster presentation and has not been peer-reviewed. The study states it is an RCT but the poster contains limited information regarding the study protocol, patient demographics and how the study was undertaken.
How was the study funded?	Funded by the Academic Teaching Hospital of the University of Heidelberg, NanoVibronix provided the devices only and did not directly fund the study.

Zalut	
How are the findings relevant to the decision problem?	This open label non-comparative study was conducted in a relevant population consisting of patients requiring short-term catheterisation as detailed in the decision problem. The study showed that the UroShield had a positive effect on patient reported pain, itching, burning and spasm as well as overall well-being.
Does this evidence support any of the claimed benefits for the technology? If so, which?	This supports the claimed benefits relating to health related quality of life and reduction in the catheter-related pain, spasm and discomfort.

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Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The data is published on the company website and has not been peer-reviewed or published in a scientific journal. The data only contains limited information regarding the study protocol, patient demographics and how the study was undertaken. The patients did not have long term indwelling catheter usage as the catheter was used post-discharge from the ED and device use time ranged from 4 to 12 days.
How was the study funded?	NanoVibronix provided the devices only and did not directly fund the study.

Da Silva, 2020	
How are the findings relevant to the decision problem?	The data is taken from real world use of the device in the NHS and is gathered from a relevant patient population with relevant outcomes as detailed in the decision problem. There was no comparator group.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence published supports the claim to reduce CAUTI through the reduction of UTI associated with urinary catheters. Any reduction in CAUTI is expected to translate to a reduction in costs for the NHS from both a reduction in the need for NHS resources (reduced catheter changes) as well as antibiotic use. The study also provides evidence to support the quality of life and catheter associated pain, spasm and discomfort and is supported by qualitative thematic analysis on patient feedback demonstrating an overall improvement in well-being. The study also supports the ease of implementation of UroShield in the NHS.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The data has been submitted for publication. Presently unpublished and not available on the company website. The study is non-comparative but the data is gathered from an NHS setting. The data only contains limited information regarding the study protocol, patient demographics and how the study was undertaken.
How was the study funded?	The study was in response to the NICE scientific team advice to collect data on NHS patients using UroShield. The devices have been provided to the patients by Ideal Medical Solutions through the NHS clinicians. No payments have been made to any clinicians nor patients.

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Shenfeld and Haris, 2010	
How are the findings relevant to the decision problem?	This RCT was conducted in a relevant population consisting of patients requiring short-term catheterisation in a hospital setting as detailed in the decision problem. The comparator was standard catheter care. The study showed a reduction in bacteriuria, catheter-related pain, spasm and discomfort as well as medication use in the active compared to the control group.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The RCT evidence supports the claim to reduce CAUTI through the reduction of bacteriuria associated with urinary catheters. Any reduction in CAUTI is expected to translate to a reduction in costs for the NHS from both a reduction in the need for healthcare resources as well as antibiotic use. The study also provides evidence to support a reduction in the catheter associated pain, spasm and discomfort as well as reduction in the amounts and strength of medication taken by patients.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The data is unpublished and not available on the company website. The authors report that the data on bacteriuria is limited and analysis was only possible on the data at the 3-day time point. In addition, the RCT gained approval to recruit 210 patients but due to company commercial strategy, the study was closed at 40 patients.
How was the study funded?	The study was funded by the Shaare Zedek Medical Center, Jerusalem. NanoVibronix provided the devices only and did not directly fund the study.

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6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

No device alerts or field safety notices associated with the UroShield product have been identified within either the MHRA, FDA or TGA databases.
Search strings – UroShield, NanoVibronix

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Markowitz 2018
The study reported no adverse events in either of the UroShield or Control groups.

Nagy 2011
The catheter had to be removed prematurely in case of 2 patients in the UroShield group (1 blockage and 1 bleeding) and in case of 2 patients in the control group (1 balloon error and 1 bleeding). It is believed that the removal was due to catheter related events as it is not stated in the poster that any adverse events were directly related to the UroShield device.

Ikinger 2007
The poster reported that the UroShield proved to be safe and well tolerated with no difference in reported adverse events between the 2 groups

Shenfeld and Haris 2010
Adverse Events
In terms of safety, there were similar numbers of adverse events in both groups all classified as unrelated to the device.

18 adverse events were reported during the trial: 10 in the control group and 8 in the active group. The adverse events were followed by such conditions as: hypertension, anaemia, temperature, bladder pain, catheter extruded, fever, leukocyturia and alike. The PI determined that the adverse events are unlikely to be related to the UroShield device. All patients completely recovered at the end of the trial.

Serious adverse event (SAE)
1 serious adverse event was reported during the trial with a patient from control group and was related to prolonged ventilation. The event was considered as unlikely to be related to the UroShield device and patient completely recovered.

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7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

The following four studies were selected for the quantitative evidence synthesis: Markowitz (2018), Nagy (2011), Shenfeld (2010) (unpublished), and Zillich (2014). These studies were chosen because they all reported data on bacteriuria or CFU counts. There were substantial differences in the patient populations (short vs long term catheters), reported results (infection with or without symptoms, and/or bacteriuria/CFU), length of follow-up (ranged between 3 and 90 days), and type of control (sham device, no device, or Trimethoprim 2x200mg per day). Because of these differences and the small number of studies available, only a limited number of pair-wise meta-analyses were conducted and these should be interpreted with caution and with consideration of the differences in study design.

Three pair-wise meta-analyses were conducted in the following populations:

1) People with a catheter (All four studies).
2) People with a long-term catheter (Markowitz and Nagy).
3) People with a short-term catheter (Shenfeld and Zillich).

In all three meta-analyses, the outcome of interest was significant bacterial infection, defined as bacteriuria or counts >10,000/ml by the authors. This infection may or may not be symptomatic. The outcome is reported as the number of patients with “significant bacterial infection” in the treatment (UroShield) and control group. The total number of participants in each of the treatment and control groups were also extracted.

Markowitz reported data at 30 and 90 days. Only the data from 30 days was used to reduce the heterogeneity in follow-up lengths between the studies.

Meta-analyses were performed using the ‘metan’ command in Stata v16.1, which estimates risk ratios from the counts of events and non-events in each group, and then pools these risk ratios using the Mantel-Haenzel method

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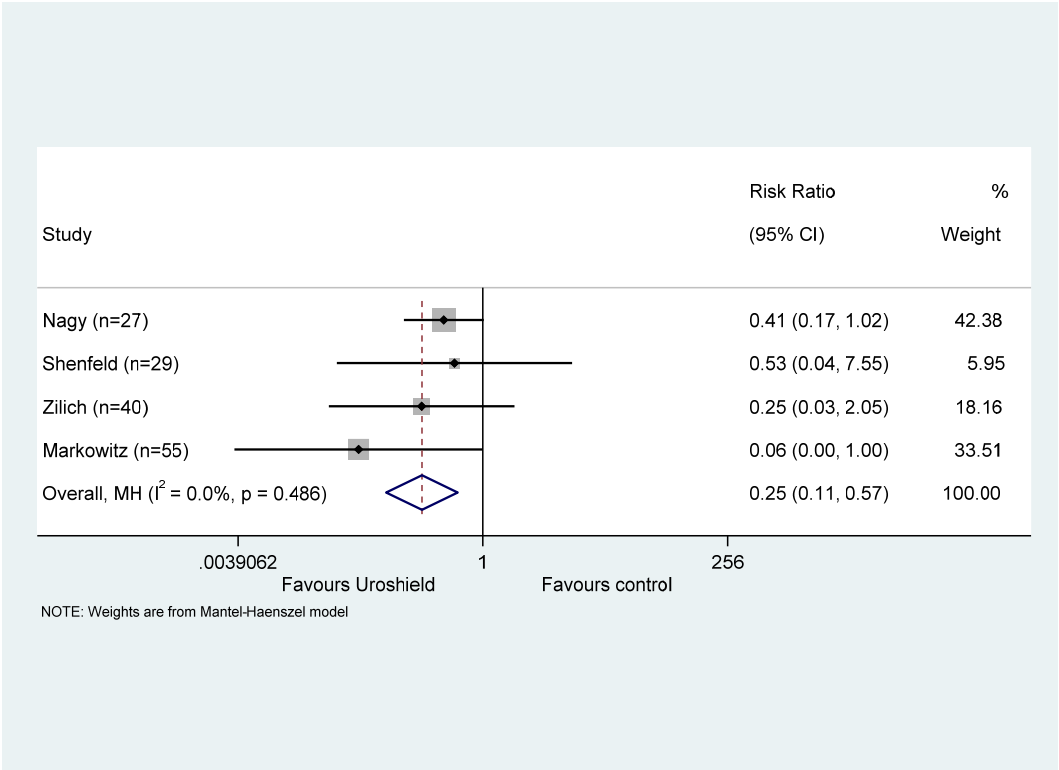
Report all relevant results, including diagrams if appropriate.

People with a catheter

The combined risk ratio for significant bacterial infection in all four studies was 0.252 (95% confidence interval = 0.112 to 0.566; p-value = 0.001) in favour of UroShield. The I^2 heterogeneity was 0.0%.



People with a long-term catheter

The combined risk ratio for significant bacterial infection in the two long-term catheter studies was 0.230 (95% confidence interval = 0.091 to 0.587; p-value = 0.002) in favour of UroShield. The I^2 heterogeneity was 59.6%.

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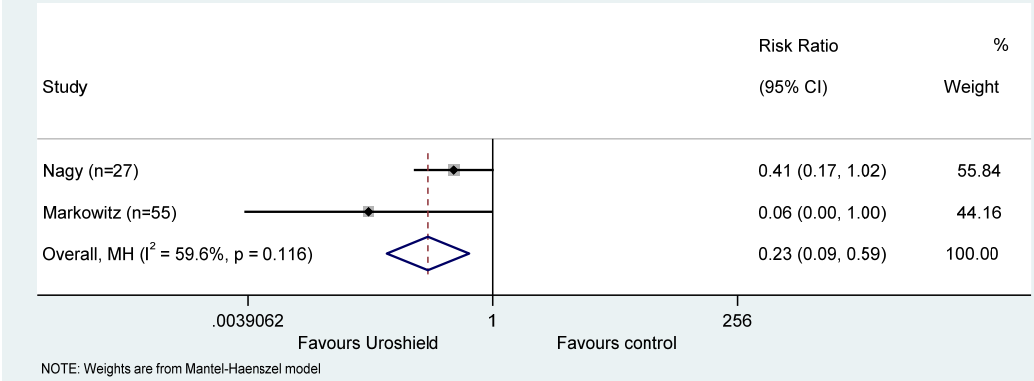
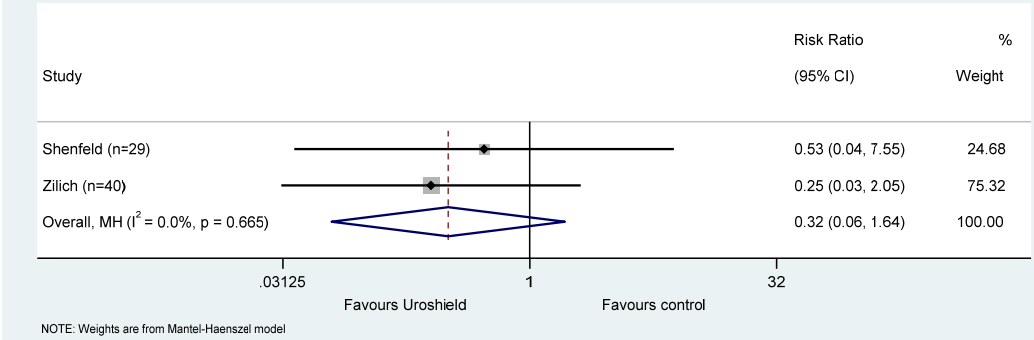


People with a short-term catheter

The combined risk ratio for significant bacterial infection in the two short-term catheter studies was 0.318 (95% confidence interval = 0.062 to 1.638; p-value = 0.171) in favour of UroShield. The I^2 heterogeneity was 0.0%.



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Explain the main findings and conclusions drawn from the evidence synthesis.

The results suggest that UroShield reduces the risk of significant bacterial infection by approximately 75% in people with a catheter. The estimate is similar (77%) in people with a long-term catheter, and slightly lower 68% in people with a short-term catheter. These findings were statistically significant in people with a catheter overall and in long-term catheters, but it was not statistically significant in people with a short-term catheter.

As noted above, there are important differences in terms of study design. However, the large effect sizes and low statistical heterogeneity, despite of these study designs, provide encouraging evidence of the effectiveness of UroShield in reducing significant bacterial infection compared with the control groups tested.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Enter text.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The clinical evidence is drawn from 7 studies (a mix of RCT and observational studies) undertaken in the relevant patient population that included people requiring urinary catheterisation for any reason in either the short (approximately 3-28 days) or long term (>28 days according to current NICE guidelines). The main clinical benefit is a reduction in bacteriuria in catheterised patients (six out of seven studies) and four of the comparative studies were suitable for evidence synthesis. This showed a decrease in significant bacterial infection (defined as either bacteriuria or absolute CFU counts reported by the authors) in the UroShield group in comparison to the control group. When all catheterised patients are included in one group, the RR is 0.252 (95% CI 0.112-0.566, p=0.001). The evidence can be further broken down into either short term catheterisation (RR 0.318 ‘0.062-1.638, p=0.171) or long term catheterisation (RR 0.230, [0.091-0.587, p=0.002). The studies (n=4) also report the UroShield has a significant effect on reduction in catheter-related pain, spasm and discomfort.

Additional outcomes include a reduction in biofilm formation on catheters and a reduction in UTIs and association medication. UroShield can also reduce the need for prophylactic antibiotics such as trimethoprim (Zillich et al, 2014). Da Silva reported that therapeutic antibiotic usage, catheter changes and blockages could all be reduced after 12 weeks of UroShield use in the NHS and user feedback reported positive outcomes to overall patient well-being and tolerability of the device.

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Three of the studies reported on adverse events which included standard catheter related AE such as catheter blockage, bleeding, bladder pain etc. None of the AE were classified as being related to the use of the UroShield device.

The clinical evidence base demonstrates the clinical benefit and safety of the UroShield in patients with a urinary catheter.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The evidence base is directly relevant to the scope as it covers the PICO as described in the decision problem. The population description is broad and covers all people with a urinary catheter in any setting. The data covers both short and long term catheterisation and hospital or community settings. The evidence synthesis indicates a significant effect on reduction of bacteriuria with the UroShield group, particularly in the longer-term catheterised patients who are most at risk of repeated UTI and CAUTI. Any intervention that can impact on CAUTI levels will in turn have a positive impact on costs, both for health care resource use, and medication costs such as antibiotic prescriptions. It should be noted that data to support resource use etc in the NHS (Part 2) will be drawn from publicly available data.

The evidence base is drawn from seven studies of which one is a published peer-reviewed article, one is under consideration at a peer-reviewed journal, one is an unpublished RCT investigators report and four are conference abstracts. Despite the low quality of some of the non-peer-reviewed abstract evidence, it was still judged possible to undertake some limited evidence synthesis on the primary outcome, though caution on the interpretation would be advised due to the small numbers of studies and quality of the data.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

There is only 1 report based on patients in the UK (Da Silva, submitted). This UK based real world study was suggested by the NICE Scientific team following their review of the data and was conducted in 2020. This is a non-comparative data derived from real world use of the UroShield in long-term catheterised patients in a community setting that demonstrated a reduction in UTI, catheter-associated pain and discomfort, catheter changes and blockages. The other six studies were based in Europe, USA or Israel and fully support the UK-based data with equivalent populations and outcomes. In addition, the criteria on whether a patient has a clinical significant bacterial infection (bacteriuria), is the same whether defined by the CDC (USA) or Public Health England. It is therefore considered that the evidence base presented here is generalisable across the NHS.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The decision problem extends to all people with a catheter. However, the evidence base is strongest in the community population of people with long term indwelling catheters (>30 days) and this is supported by the evidence synthesis. It is known that duration of catheterisation is a key risk factor for CAUTI and this would be one of the primary criteria in identifying patients who would benefit most from UroShield. It is expected that most patients in the community will have need of long-term or even lifetime indwelling catheterisation. Within the hospital setting where patients are often catheterised in the short term, those who are on ICU/CC or are likely to be catheterised for more than 3 days are also likely to benefit from

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UroShield. Patients on ICU/CC are often more likely to be given prophylactic antibiotics and UroShield may reduce this need which could have an impact on over anti-microbial strategies within NHS Trusts. It is unlikely that patients catheterised for fewer than 2 days would benefit so anticipated length of stay may be a useful factor to include when considering UroShield in hospital patients.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The main strengths of the evidence base lies in the equivalent outcomes across the studies, including two RCT and 2 controlled observational studies, enabling some evidence synthesis to be undertaken. The evidence synthesis demonstrates a significant reduction in bacterial infection in both all patients with a catheter and more specifically in those with a long term indwelling catheter. Unusually for device studies, two of the studies were able to be “technology-blinded” i.e. used a sham device that did not emit the surface acoustic waves but would emit a similar hum such that patients would be unaware their device was inactive. The evidence base does have a number of limitations, primarily the fact that five of the seven studies have not been subject to a non-peer review process. In addition, four of the studies are conference abstracts with limited details and information being reported and are therefore judged to be low quality.

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9 References

Please include all references below using NICE's standard referencing style.

Adler S.N. (2009) Evaluation of safety and efficacy of a new device intended to decrease pain and discomfort associated with NG Tube use. Gastroenterology. 136 (5):

Appelbaum I.; Levi Y.; Shenfeld O.Z. (2010) The effect of acoustic energy induced by UroShield on foley catheter related trauma and inflammation in a rabbit model. European Urology, Supplements. 9 (2):107

Childers C; Edsall C; Gannon J; Whittington A; Muelenaer A; Rao J; Vlaisavljevich E. (2021) Focused Ultrasound Biofilm Ablation: Investigation of Histotripsy for the Treatment of Catheter-Associated Urinary Tract Infections (CAUTIs). IEEE transactions on ultrasonics, ferroelectrics, and frequency control; May 2021

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Hazan, Zadik; Zumeris, Jona; Jacob, Harold; Raskin, Hanan; Kratysh, Gera; Vishnia, Moshe; Dror, Naama; Barliya, Tilda; Mandel, Mathilda; Lavie, Gad. (2006) Effective prevention of microbial biofilm formation on medical devices by low-energy surface acoustic waves. Antimicrobial agents and chemotherapy. 50 (12): 4144-4152

Ikinger U, Zillich S, and C. Weber. Biofilm prevention by surface acoustic nanowaves: a new approach to urinary tract infections. Poster publication

Kopel, Moran; Degtyar, Elena; Banin, Ehud. (2011) Surface acoustic waves increase the susceptibility of Pseudomonas aeruginosa biofilms to antibiotic treatment. Biofouling. 27 (7): 701-710

Loike, John D; Plitt, Anna; Kothari, Komal; Zumeris, Jona; Budhu, Sadna; Kavalus, Kaitlyn; Ray, Yonatan; Jacob, Harold. (2013) Surface acoustic waves enhance neutrophil killing of bacteria. PloS one. 8 (8): e68334

Markowitz S, Rosenblum J, Goldstein M, Gadagkar R, and L. Litman. (2018) The Effect of Surface Acoustic Waves on Bacterial Load and Preventing Catheter- associated Urinary Tract Infections (CAUTI) in Long Term Indwelling Catheters Medical and Surgical urology. 7 (4): 1-3

Nagy K.; Koves B.; Tenke P. (2011) The effectiveness of acoustic energy induced by UroShield device in the prevention of bacteriuria and the reduction of patients' complaints related to long-term indwelling urinary catheters European Urology, Supplements. 10 (2):163-164

Rosenblum J.; Markowitz S.; Goldstein M. (2017) Surface acoustic waves prevent bacterial colonization in indwelling urinary catheters. European Urology, Supplements. 16 (3)

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Shenfeld, O and Haris, D. (2010) The use of the UroShield device in patients with indwelling urinary catheters. Clinical Trial Report, unpublished

Smith DRM, Pouwels KB, Hopkins S, Naylor NR, Smieszek T, and Robotham JV. (2019) Epidemiology and health-economic burden of urinary catheter-associated infection in English NHS hospitals: a probabilistic modelling study. J Hospital Infection 103 (1):44-54

Zalut. The effect of UroShield on pain and discomfort levels in patients released from the emergency room with urinary catheter due to urinary incontinence. NanoVibronix Website

Zillich S, Weber, C and U. Ikinger. (2014) Replacement of antibiotic therapy by UroShield device in subjects with urinary catheter following radical prostatectomy. NanoVibronix Website

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	17th May 2021
Date span of search:	2000 to present
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	

NICE HDAS platform was used to perform the literature search.
Search strings were drawn from the following phrases or words

Population – Urinary catheter, long term, indwelling urinary catheter,

Intervention – UroShield, ultrasonic waves, acoustic shield, Nanovibronix,

Comparator – standard of care

Outcomes – bacteriuria, CFU, bacterial counts, colonis(z)ation, biofilm, infection , UTI, CAUTI, pain, spasm, discomfort, quality of life, adverse events,

Limits: 2000-2021, English

Platform: NICE HDAS

Output – all references identified below were exported to Excel for sifting by title and abstract and then by full text to identify relevant literature according to the inclusion/exclusion criteria.

Published studies

Date	Database	Terms	Results
17/05/2021	Medline	(nanovibronix OR UroShield).ti,ab	1 result
17/05/2021	Medline	((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp ULTRASONICS/ OR (UroShield OR nanovibronix).ti,ab OR (acoustic shield OR surface acoustic waves).ti,ab)) [DT 2000-2021] [Languages English]	4 results
17/05/2021	Medline	((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp ULTRASONICS/ OR (UroShield OR nanovibronix).ti,ab OR (acoustic shield OR suface acoustic waves).ti,ab OR (ultrasound waves OR ultrasound).ti,ab)) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation)) [DT 2000-2021] [Languages English]	92 results

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17/05/2021	Medline	exp "URINARY CATHETERS"/ AND (ultrasound waves).ti,ab	0 results (zero)
17/05/2021	Medline	((((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp "URINARY TRACT INFECTIONS"/ OR exp BACTERIURIA/ OR (bacter* CFU).ti,ab OR (bacterial colonisation OR bacterial colonization).ti,ab OR (biofilm).ti,ab OR (CAUTI).ti,ab OR (pain OR spasm OR discomfort).ti,ab OR (quality of life).ti,ab OR (adverse events).ti,ab)) AND (exp ULTRASONICS/ OR (UroShield OR nanovibronix).ti,ab OR (acoustic shield OR surface acoustic waves).ti,ab OR (ultrasound waves OR ultrasound).ti,ab)) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation)) [DT 2000-2021] [Languages English]	33 results
17/05/2021	PubMed	(nanovibronix OR UroShield).ti,ab	2 results
17/05/2021	PubMed	(((urinary catheter* OR foley catheter* OR urethral catheter* OR ureteral catheter*).ti,ab OR (urinary catheter OR foley catheter OR urethral catheter OR ureteral catheter).ti,ab OR (urinary catheterization OR foley catheterization OR urethral catheterization OR ureteral catheterization).ti,ab) AND (ultrasound OR ultrasound waves OR ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound).ti,ab) AND (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life OR adverse events).ti,ab AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).	274 results
17/05/2021	EMBASE	(UroShield OR nanovibronix).ti,ab [DT 2000-2021] [Languages English]	5 results
17/05/2021	EMBASE	(((exp "UROLOGICAL CATHETER"/ OR exp "URINARY CATHETER"/ OR (long term urinary catheter).ti,ab OR exp "BLADDER CATHETERIZATION"/ OR (indwelling urinary catheter).ti,ab) AND ((UroShield OR nanovibronix).ti,ab OR ((surface acoustic waves OR acoustic waves).ti,ab OR (ultrasound OR ultrasound waves).ti,ab OR (ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound).ti,ab))) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).ti,ab) [DT 2000-2021] [English language]	402 results
17/05/2021	EMBASE	((exp "URINARY TRACT INFECTION"/ OR (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life OR adverse events).ti,ab) AND (((exp "UROLOGICAL CATHETER"/ OR exp "URINARY CATHETER"/ OR (long term urinary catheter).ti,ab OR exp "BLADDER CATHETERIZATION"/	180 results

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		OR (indwelling urinary catheter).ti,ab) AND ((UroShield OR nanovibronix).ti,ab OR ((surface acoustic waves OR acoustic waves).ti,ab OR (ultrasound OR ultrasound waves).ti,ab OR (ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound).ti,ab))) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).ti,ab)) [DT 2000-2021] [English language]	
17/05/2021	Cinahl	((exp "CATHETERS, URINARY"/ OR exp "URINARY CATHETERIZATION"/ OR indwelling urinary catheter OR long term urinary catheter) AND (UroShield OR nanovibronix OR surface acoustic waves OR acoustic waves OR ultrasound OR ultrasound waves OR ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound)) [DT 2000-2021] [Languages eng]	120 results
17/05/2021	Cinahl	(((exp "CATHETERS, URINARY"/ OR exp "URINARY CATHETERIZATION"/ OR (indwelling urinary catheter OR long term urinary catheter).ti,ab) AND ((UroShield OR nanovibronix).ti,ab OR (surface acoustic waves OR acoustic waves OR ultrasound OR ultrasound waves OR ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound).ti,ab)) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation)) [DT 2000-2021] [Languages eng]	43 results
17/05/2021	Cinahl	(((exp "URINARY TRACT INFECTIONS, CATHETER-RELATED"/ OR (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life OR adverse events).ti,ab) AND ((exp "CATHETERS, URINARY"/ OR exp "URINARY CATHETERIZATION"/ OR (indwelling urinary catheter OR long term urinary catheter).ti,ab) AND ((UroShield OR nanovibronix).ti,ab OR (surface acoustic waves OR acoustic waves OR ultrasound OR ultrasound waves OR ultrasonic OR ultrasonic waves OR ultrasonic vibration OR pulsed ultrasound OR low intensity pulsed ultrasound).ti,ab))) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).ti,ab) [DT 2000-2021] [Languages eng]	8 results

Ongoing studies

DATE	DATABASE	TERMS	RESULTS
18/05/2021	www.clinicaltrials.gov	UroShield	6 results 1 study withdrawn 1 study enrolling by invitation 4 studies with unknown status (1 on endotracheal tubes, 2 on long term indwelling catheters, 1 on percutaneous catheters)
18/05/2021	ISRCTN	UroShield	No results
		Nanovibronix	No results

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18/05/2021	PROSPERO	UroShield	No results
		Nanovibronix	No results
20/05/2021	NIHR CRN portfolio	UroShield	1 result – Wilks study as detailed in Table 3

Grey Literature

DATE	DATABASE	TERMS	RESULTS
18/05/2021	www.greylit.org	UroShield Nanovibronix	No results
18/05/2021	www.opengrey.eu	UroShield Nanovibronix	No results

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

The company website was searched to identify further clinical evidence that had not been published in peer-reviewed literature.

Non-peer reviewed, company held reports, n=5

Inclusion and exclusion criteria:

Inclusion – use of UroShield in relevant patient population (catheterised patients)

Exclusion – use of non-UroShield devices, use of ultrasound for imaging, histotripsy, non-human studies including in vitro laboratory studies, non-research articles (e.g. editorials, letters, comments etc)

Data abstraction strategy:

The data from peer-reviewed published articles was abstracted using the Cochrane Collaboration tool for data extraction

The data abstraction was conducted by Sarah Bolton and reviewed by clinical and product experts at Nanovibronix

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Loike et al, 2013	Experimental study: surface acoustic wave device from Nanovibronix	Article reports results from both laboratory and animal-based experiments with no clinical data included.	Text
Kopel et al, 2011	Experimental study: surface acoustic wave device from Nanovibronix	Article reports results from laboratory experiments with no clinical data included	Text

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Rosenblum et al, 2017	Double-blind RCT using UroShield	The reference is an abstract based on the patient population reported in Markowitz et al, 2018	Text
Appelbaum et al, 2021	Experimental study: effect or UroShield on catheter-induced trauma in rabbits	Article reports results from both laboratory and animal-based experiments with no clinical data included.	Text
Childers et al 2021	Experimental study: effect of histotripsy on catheter biofilms	Histotripsy is a pulsed focused non-invasive high frequency ultrasound treatment to reduce bacteria viability. This is not the same as the UroShield low frequency/low intensity surface acoustic wave technology.	Text
Adler, 2009	Healthy volunteer study using NGShield (Nanovibronix)	Study uses the NGShield product from Nanovibronix which is based on the same surface wave acoustic technology but is not the same device as the UroShield	Text
Hazan et al, 2006	Experimental study: surface acoustic wave device from Nanovibronix	Article reports results from both laboratory and animal-based experiments with no clinical data included.	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

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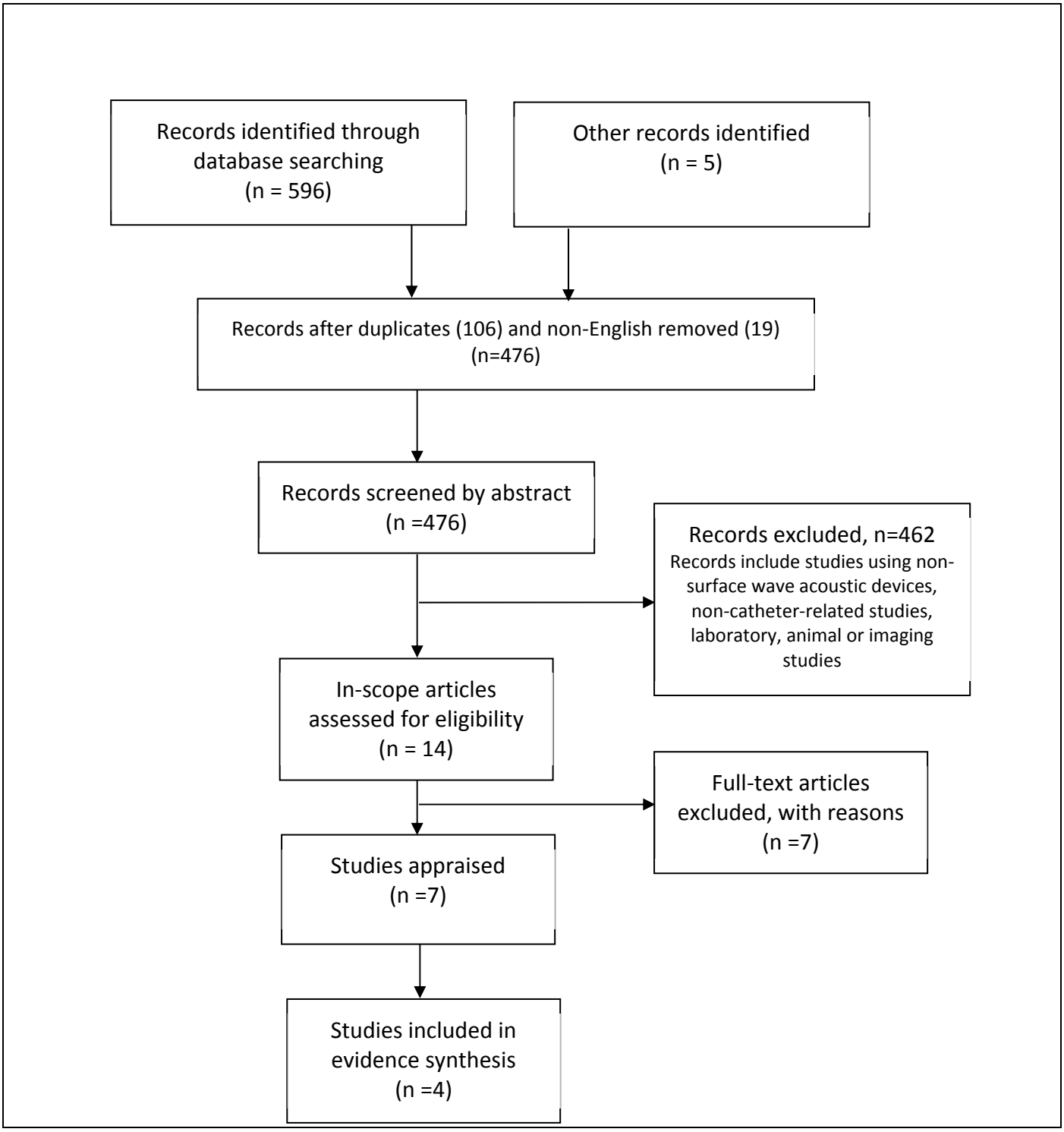

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Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

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Appendix B: Search strategy for adverse events

Date search conducted:	17/05/2021
Date span of search:	2000-present
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The literature searches detailed in Appendix A include the term “adverse event” and were used to identify any relevant literature.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
No additional searches were done.	
Inclusion and exclusion criteria:	
Include – use of UroShield, report of adverse events Exclude – studies where UroShield has not been used, non-clinical studies	
Data abstraction strategy:	
See Appendix A	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

No further studies other than those described in Appendix A, clinical evidence, were identified.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

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See Appendix A

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Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

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Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	26/5/2021
Print:	Brian Murphy	**Role / organisation:**	CEO-NanoVibronix, Inc
Contact email:			

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT476 UroShield for preventing catheter associated urinary tract infections

Company evidence submission

Part 2: Economic evidence

Company name	NanoVibronix Inc
Submission date	28 June 2021
Contains confidential information	No

Contents

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1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		67
Number of studies identified as being relevant to the decision problem.		0
Of the relevant studies identified:	Number of published studies.	0
	Number of abstracts.	0
	Number of ongoing studies.	0

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List of relevant studies

No relevant studies were identified by the literature searches as being directly relevant to the Uroshield device decision problem. However, the evidence synthesis meta-analysis performed in Part 1 (using 4 previously identified records; 1 published abstract and 3 unpublished studies, see Part 1 Form) was used to inform the modelling.

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2 Details of relevant studies

No relevant studies were identified in the literature. See Part 1 form for meta-analysis using 4 identified records.

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3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Patients who have an indwelling urinary catheter inserted who are in an acute or community setting.

In the **acute setting**, the following groups were considered:

All patients catheterised

Patients with short term catheterisation (<28 days)

Patients with long term catheterisation (>28 days)

Patients catheterised in ICU

In the **community setting,** the following groups were considered:

All patients with a catheter

Patients with recurrent CAUTI (based upon the EAU guidelines on UTI of two CAUTIs in a six month period or three in a year (https://uroweb.org/guideline/urological-infections/))

For patients in the acute setting, it is acknowledged that it could, in some cases, be difficult to ascertain exactly how long a person will require a catheter when it is inserted. However, Epic 3 Guidelines on preventing hospital acquired infection specifically provides recommendations for short term catheterisation defined as <28 days which implies that such patients can be, at least in most cases, determined at the time the catheter is inserted.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Technology

UroShield device with actuators replaced every 30 days in addition to current hygiene procedures to reduce CAUTI (SoC)

Comparator

Current hygiene procedures to reduce CAUTI (SoC). It is assumed prophylactic antibiotics are not routinely used in line with recommendations in NG113

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Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The model structure was chosen to be only as complex as required to capture the key difference between UroShield and SoC i.e. the risk of developing a CAUTI. There is a fixed probability of CAUTI developing into a CABSI and a fixed probability CABSI ends up in death. Outside of death, there are no long-term consequences considered in the model. As CAUTI is considered a one off event in hospital, a decision tree was a suitable model for hospitalised populations considered. For catheterised patients in the community, CAUTI was considered to only occur at most once every month and future CAUTIs and outcomes from CAUTIs were considered to be independent of previous CAUTIs. A decision tree was therefore also suitable for the community population considered.

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Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Short term catheterisation is <28 days.	In line with EPIC 3 Guidelines.	Lovejoy 2014
The UroShield driver has a two year life-span and each driver can be re-used for an individual patient or for different patients.	In line with warranty provided for device.	NanoVibronix
Each UroShield actuator has a life-span of 30 days. The actuator is replaced on the existing catheter every 30 days.	In line with product information.	NanoVibronix
There are no training costs in the model and no nursing time has been included for connecting the driver and attaching the actuator when inserting a new catheter.	The UroShield driver connects to existing catheters with no significant training required. The time to attach the driver and replace the actuator when necessary is negligible.	Text
The efficacy of UroShield in preventing CAUTI is the same regardless of setting.	The mode of action of UroShield is such that efficacy should be independent of setting (acute, ICU or community).	

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Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results (base case)	Range or distribution (used in sensitivity analysis)	How are these values used in the model?
Rate of CAUTI				
Acute setting				
All patients	Smith et al	3.80%	3.0%-4.7%	Rate of CAUTI without UroShield
<28 days catheterisation	Smith et al	3.45%	+-25%	Rate of CAUTI without UroShield
>28 days catheterisation	Smith et al	10.17%	+-25%	Rate of CAUTI without UroShield
ICU	Smith et al	3.8%	3.0%-4.7%	Rate of CAUTI without UroShield
Community setting (monthly rates)				
All patients	Getliffe & Newton	8.5%	8.5%-10%	Rate of CAUTI without UroShield
Recurrent CAUTI only	Based on 3 in 12 months as per definition of recurrent. Range can be no lower than 25%. An upper bound of 33% was used to represent the alternative definition of recurrent of two UTIs in six months	25%	25%-33%	Rate of CAUTI without UroShield

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CAUTI sequelae				
Probability CAUTI develops into blood stream infection (CABSI)	Smith et al	4.80%	4.10%-6.30%	Applied when CAUTI occurs
Death from blood stream infection	Smith et al	19.50%	18.80%-20.5%	Applied when CABSI occurs
Relative risk of CAUTI with UroShield	Meta-analysis of relative risk of bacteriuria with UroShield	0.252	0.112-0.566	Applied to rates of CAUTI without UroShield
First line failure of antibiotics (community CAUTI)	NICE CG139	0.080	0.060-0.100	Applied when community CAUTI occurs
Multi drug resistant CAUTI (community)	NICE CG139	0.060	0.040-0.080	Applied when community CAUTI occurs
Additional length of stay in ICU with ICU onset CAUTI	Chant et al	2.3	2.0-2.6	Applied when ICU onset CAUTI occurs
Days catheterised (hospital setting only)				
All patients	Assumption	10	+-25%	Applied to work out cost of UroShield

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<28 days catheterisation	Assumption	7	+-25%	Applied to work out cost of UroShield
>28 days catheterisation	Assumption	42	+-25%	Applied to work out cost of UroShield and risk of CAUTI
ICU	Assumption	10	+-25%	Applied to work out cost of UroShield

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

Not applicable

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification

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Time horizon	In hospital setting, whilst a patient is catheterised (a mean no greater than 42 days in the model). In the community setting, a one month time horizon was chosen.	Long enough to model key differences with UroShield.
Discount rate	0%	Time horizon less than 12 months
Perspective (NHS/PSS)	NHS	PSS costs will accrue with consequences of blood stream infection but could not be quantified.

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Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

NanoVibronix undertook a systematic search of literature to identify rates of CAUTI in the NHS in England (both in the community and hospital settings).

Whilst the search strategy identified over 700 studies, only one robust study on CAUTI rates in English hospitals was found. Smith et al in a study funded by Public Health England reported a HES data analysis of CAUTI rates from 5.2m inpatients in England in 152 Acute Trusts in 2016/17. Although the only study found, the comprehensiveness of the study in terms of volume of patients and trusts makes this analysis a landmark study on CAUTI rates, specifically in England. As a recent study, it also captures the reductions in the rate of CAUTI that may have been seen since the publication of the EPIC3 Guideline and NICE recommendations on reducing CAUTI.

Smith et al reported that 3.8% of all patients with a catheter developed *hospital onset* CAUTI which increased with time of catheterisation from 3.1% for patients with LOS of 2 days to 13.2% for patients with LOS of 40 or more days. To estimate a CAUTI rate at a specific point in time, the assumption was made by NanoVibronix that mean LOS for those with a LOS of over 40 days would be 60 days. This assumption was considered conservative as the longer the assumed total LOS the lower the daily risk of CAUTI would be (i.e. the risk of 13.2% would be spread over a longer time period).

The value of 3.8% as the overall risk of CAUTI in all patients from Smith et al was used as the CAUTI rate for all patients in the model. Evidence on length of catheterisation of all patients catheterised could not be identified and was not reported in Smith et al. However, for patients catheterised for less than 14 days in the hospital setting, an NIHR funded HTA by Pickard et al of a trial of the effectiveness of different types of catheter in stopping CAUTI in patients catheterised for less than 14 days in the hospital setting (the Catheter trial), was referenced by Smith et al. This study reported the mean length of catheterisation in the trial (95% of patients were elective rather than emergency admissions) of just under three days. As patients with more than 14 days catheterisation were excluded and NanoVibronix considers it plausible that non-elective patients may require longer catheterisation, a mean duration of 10 days catheterisation was considered a conservative assumption for mean length of catheterisation for all patients catheterised. NanoVibronix highlights that a longer length of catheterisation is a conservative assumption (i.e. a pessimistic assumption that will negatively impact the cost-effectiveness of UroShield) as the risk of CAUTI is fixed in the model for the 'all patients' population regardless of length of stay and increasing the length of stay just increases the cost of UroShield.

As Smith et al did not report CAUTI rates specifically in ICU and the literature search did not identify any ICU specific rates of CAUTI in England or the UK, the modelling assumes that ICU rates and length of catheterisation are the same as for the average for all patients in the hospital. Evidence identified in the literature searches from small studies outside of the UK (e.g. Agodi et al 2011) suggests CAUTI rates in ICU are likely to be substantially higher than 3.8%. However, the definition of ICU can differ across countries and as such a conservative approach was taken in using the allpatients rate which at least relates to English patients if likely an underestimate of the true CAUTI rate in English ICUs.

The CAUTI rate for short term catheterisation (<28 days) has to be between the 3.1% rate reported in Smith et al at for two days catheterisation and the 3.8% reported for all patients. For simplicity a rate halfway

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between these values was chosen (i.e. 3.45%) with an assumption that short term catherization (<28 days) would be on average for 7 days with similar reasoning as for the length of stay for all patients.

The CAUTI rates for long term (>28 days) catheterisation was estimated by a linear interpolation between 3.1% at two days from Smith et al and the 13.2% at an assumed 60 days with assumed the length of stay for all patients and for long term catheterisation (>28 days) of 42 days. The choice of 42 days for long term catheterisation was to ensure that an additional actuator would be required for such patients which increases the costs of UroShield and results in a conservative assessment (i.e. higher estimate) of the costs of UroShield.

Whilst the CAUTI rates in Smith et al are the best available, they are supported by the EPIC 3 Guideline, for example, which states that 30% of catheterised patients will develop bacteriuria between 2-10 days of catheterisation and 24% of these will develop symptomatic CAUTI (so approximately 7% of catheterised patients will develop symptomatic CAUTI by 10 days). The same Guideline also reports that there is a 5% day on day increase in bacteriuria such that by 30 days almost all catheterised patients will develop bacteriuria with a 24% risk of developing symptomatic CAUTI. Improvements in catheter care since the production of the Guideline in 2014 may be why rates reported in Smith et al are lower. The CAUTI rates in Smith et al are in line with studies from other countries such as Letica-Kriegal et al who examined CAUTI rates in six US hospitals between 2012 and 2016 and reported CAUTI rates of 2.70% at ten days, 11.8% at 30 days and 28.2% at 60 days.

For community CAUTI, for recurrent, the monthly rate is determined by the definition of recurrent and to be conservative, NanoVibronix have chosen the lower of the potential rates within the definitions (i.e. three in a year rather than two in six months). As patients with a lower rate than three CAUTIs in a year would not be considered recurrent this is as low a rate as could be chosen. In reality, patients with recurrent CAUTI are likely to have higher rates of CAUTI than has been modelled. For all patients with long term indwelling catheters in the community, a monthly CAUTI rate of 8.5% was taken from a study by Getliffe & Newton. Although this study was from 2006, it was the latest study that could be identified that was UK, community based CAUTI.

The risk of bacteraemia and the risk of death for bacteraemia was taken from Smith et al as this was the most robust and recent UK source for these values.

The risk reduction with UroShield has been taken from the meta-analysis undertaken from this submission, with the reduction in bacteriuria being assumed to be equivalent to the reduction in CAUTI for all patients catheterised. This rate was higher than the meta-analysis of just long-term catheterisation and so gives a conservative estimate in the community setting in particular.

Given the direct link between bacteriuria and CAUTI (EPIC 3 Guideline) NanoVibronix thinks this is reasonable but also conservative. In the most robust studies looking at the efficacy of UroShield on actual CAUTI UroShield was significantly more effective than suggested by the NMA. Markowitz et al found a 100% reduction in infection in the month when UroShield was actually used in the trial and the real world data in Da Silva reported an 85% reduction in infections over 12 weeks.

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Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

The UroShield driver cost is £349, the cost of the actuators is £50 and must be replaced every 30 days. The UroShield driver has a life expectancy of two years and costs per patient in the hospital setting have been pro-rated based upon the number of days of catheterisation and assuming the device can be rapidly redeployed to another patient the day after the previous patient no longer requires the driver. Actuators cannot be reused between patients and so each patient will require a new actuator when first catheterised.

If the list price is not used in the model, provide the price used and a justification for the difference.

Not relevant

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

There are no current NHS reference costs specifically for treating CAUTI.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

Four outcomes in the model incur NHS resource use:

- Hospital onset CAUTI
- Community onset CAUTI
- ICU onset CAUTI
- Bacteraemia

The literature search described in Section 1 identified

Hospital onset CAUTI

It was pointed out in the EPIC 3 Guideline that economic evidence on the impact of CAUTI is lacking. This was in 2014 and a pragmatic search of literature since then highlighted no new UK analysis of costs

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of CAUTI in the hospital setting. International evidence was identified, notably a systematic review and meta-analysis on additional costs arising for hospital acquired infections in the USA for the

Agency for Healthcare Research and Quality (AHRQ) from 2017 found that the average costs for the development of CAUTI in hospital added a mean of $13,793 to the cost of patient treatment. Whilst care must be taken in generalising costs from the USA to the UK, the review suggests that additional costs with CAUTI are likely to be significant in the UK.

Whilst acknowledging the limitation of available evidence, a figure of £1,968 is quoted per CAUTI episode in the EPIC 3 Guideline (from 2014). The source of this figure can be traced back to a study by Plowman et al from 2001 that measured the excess cost from hospital acquired infections to the NHS and reported the additional cost of UTI as £1,327 based upon data from 1994/1995 . This figure would be £2,676 after adjustment by HCHS (to 2015/16) and NHSCII (from 2015/16 to 2019/20) inflation indices. This is in line with the weighted average 2019/20 NHS Reference Cost for 'Kidney or urinary tract infections' non-elective admissions (£2,852) but for a conservative estimate the cost quoted in the EPIC 3 Guideline unadjusted for inflation was used in the analysis (£1,968).

It is noted that a value of £532 for the excess cost of CAUTI was used in the Smith et al study that provides the evidence on hospital onset CAUTI rates in the model. However, this value is taken from the NIHR HTA by Pickard et al and NanoVibronix considers that this value has been wrongly calculated from the study. The excess costs from CAUTI in Pickard et al is an estimate for patients catheterised for no more than 14 days and essentially for elective patients only who were fit enough to consent to take part in the trial. More concerning is that the excess resource use from CAUTI is actually calculated on a rate of symptomatic UTI up to 6 weeks post randomisation of 12.0%. Given the rate of symptomatic UTI at 3 days post catheter removal was 5.8% and the average length of stay was only 7-8 days in the trial, at least half of the UTIs occurred when a patient was not in hospital and could not have incurred additional hospital costs.

The excess cost of CAUTI in Smith et al is therefore not an excess cost of hospital onset CAUTI but rather an excess healthcare cost from UTI associated with hospital catheterisation up to six weeks after catheter placement, several weeks after discharge and for likely the healthiest patients hospitalised. The fact that cost is still £532 suggests the actual cost is substantially higher and supports the value in the model. Further, the evidence in the study that the majority of UTIs associated with catheterisation may happen after catheter removal suggests that the real CAUTI rate is far higher than has been assumed in the model.

Community onset CAUTI

The costs of community onset CAUTI were derived directly from CG139 who in an economic model of intermittent catheterisation included a detailed costing of treating community developed CAUTI. Whilst the resource use was based upon CAUTI developed in intermittent catheterisation, NanoVibronix considered there is no reason to assume that the costs of CAUTI would be the different for treating CAUTI in long-term indwelling catheterisation. The costs included in CG139 included initial treatment, first line antibiotic resistance, multidrug resistance and bacteraemia (both multidrug resistance and bacteraemia require hospitalisation). CG139 also assumed that the cost of replacing a CAUTI would be required the costs were all uprated to 2019/20 prices using the HSHC and NHSCII inflation indices. Real world evidence from Da Silva presented in Part 1 included qualitative feedback that patients with recurrent CAUTI in the community tend to be more likely to require significant clinical care, including hospitalisation, when being treated for CAUTI, compared to patients who rarely have CAUTI. This finding, in combination with the rate used for recurrent CAUTI in the model being as low as it can be, means the costs of CAUTI for patients with recurrent CAUTI will be conservative.

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A large and unique data set was collected in England between 2009 and 2012 for a study on catheterrelated quality of life. This included descriptive information on characteristics of the people with long

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term catheters and data on their use of health services. This study reports an analysis of these data, including the assessment of routine costs of catheter management in the community. Implications for practice are examined.

There was a total of 624 different participant IDs which had GP data. Patients returned 414 questionnaires and DNs supplied data for 337 patients.
Unplanned catheter related events occur regularly with 43% of participants accessing out of hours services and 15% accessing A&E over the 12 month period. Moreover, one third of DN visits were outside of routine scheduled care and some hospitalisations were considered avoidable. Approximately 50% of catheter related costs can be attributed to just 14.2% of catheter users. More evidence-based interventions are needed to reduce problems that result in unplanned resource use and testing such interventions should be a priority.

The study conclusion stated: "Catheter-related problems cause distress for patients, reduce quality of life, and create unplanned expenditure for the health service. Exploring ways to reduce adverse effects of catheter use would result in significant patient benefit and health service savings and is a priority". Long term catheter management in the community; user characteristics, service utilisation, costs and implications for practice. *Gage H, Williams P, Avery M, Flannery C, Fader M, 2018*

ICU onset CAUTI

Pragmatic searches identified no UK studies specifically on the additional costs associated with ICU acquired CAUTI but did identify a meta-analysis by Chant et al which identified 11 studies with 2,745 adult patients in ICU with CAUTI and 60,719 without CAUTI. Using data from 7 studies that provided evidence on length of stay, the authors found an increased length of stay with CAUTI in ICU of 12 days (9-15 days). In studies that adjusted for other predictors of length of stay, the increased length of stay was 2.3 days (2.0-2.6 days) in the fixed effect model and 8 days (minus13-28 days) in the random effects model. As a conservative assumption, the lowest value reported for increased length of stay reported in the study (2.3 days) was used in the model. The cost of an ICU bed day (£1,218) was taken from NHS reference costs. **Bacteraemia**

The cost of bacteraemia was taken from CG139 and uprated to 2019/20 prices using the HSHC and NHSCII inflation indices.

Costs used in the model are summarised in the table below

Cost item	Base case value	Range	Source
ICU bed day	£1,218.00	Reference cost so not varied	NHS reference costs (2018/19)
CAUTI			

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Community CAUTI (first line antibiotics excluding catheters))	£43.25	Based on NHS reference costs and BNF prices so not varied	CG139
Community CAUTI (second line antibiotics)	£65.23	Based on NHS reference costs and BNF prices so not varied	CG139
Community CAUTI (multi-drug resistant)	£2,410.50	Based on NHS reference costs and BNF prices so not varied	CG139
Community treated CAUTI	£372.41	Based on NHS reference costs and BNF prices so not varied	CG139
Excess cost of hospital acquired CAUTI	£1,968	+-25%	Epic 3 Guideline, Plowman et al
Excess cost of CAUTI CABSI	£3,401	£2,061-£5,613	Smith et al
Catheter change in community			
Catheter	£5.87	Not varied as BNF prices	BNF average price of
Nurse time (minutes)	15	10-20 mins	Assumption
Cost of nurse time (hours)	£89	Not varied as taken from PSSRU	PSSRU Unit Costs of Health and Social Care 2020. Band 6 district nurse. One hour of patient contact time
Total cost of catheter change	NA	NA	£28.10	

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The training requirements to be able to use UroShield are minimal with the device simply attaching to existing catheter equipment. Drivers and actuators are small and require no special storage requirements outside of existing catheter equipment.

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Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

The change in patient outcomes only result from reduction in CAUTI. The reduction in resource requirements from reduction in CAUTI with UroShield is directly related to the reduction in CAUTI. The resources/costs associated with CAUTI have been described previously.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Not relevant. No system outcomes are changed with UroShield.

Table 5 Resource use costs

Results per patient are presented for patients catheterised as part of a hospital stay. Results per patient per month are shown for patients with long term indwelling catheters in the community.

Patients in hospital – all patients catheterised

	Technology costs	Comparator 1 costs	Difference in resource uvs costs (technolo comparator 1)
Cost of resource use to implement technology	£55	£0	+£55
Cost of resource use associated with patient outcomes	£20	£81	-£61
Total costs	£75	£81	-£6

Patients in hospital – patients catheterised<28 days

	Technology costs	Comparator 1 costs	Difference in resource uvs costs (technolo comparator 1)
Cost of resource use to implement technology	£53	£0	+£53
Cost of resource use associated with patient outcomes	£19	£74	-£55
Total costs	£72	£74	-£2

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Patients in hospital – patients catheterised>28 days

	Technology costs	Comparator 1 costs	Difference in resource use costs (technology vs comparator 1)
Cost of resource use to implement technology	£120	£0	+£120
Cost of resource use associated with patient outcomes	£55	£217	-£162
Total costs	£175	£217	-£42

Patients in hospital – patients in ICU

	Technology costs	Comparator 1 costs	Difference in resource uvs costs (technolo comparator 1)
Cost of resource use to implement technology	£55	£0	+£55
Cost of resource use associated with patient outcomes	£28	£113	-£85
Total costs	£83	£113	-£29

Patients in community – all community patients catheterised

	Technology costs	Comparator 1 costs	Difference in resource uvs costs (technolo comparator 1)
	£65	£0	

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Cost of resource use to implement technology			+£65
Cost of resource use associated with patient outcomes	£8	£33	-£25
Total costs	£73	£33	+£40

Patients in community –community patients catheterised with recurrent CAUTI

	Technology costs	Comparator 1 costs	Difference in resource uvs costs (technolo comparator 1)
Cost of resource use to implement technology	£65	£0	+£65
Cost of resource use associated with patient outcomes	£24	£97	-£73
Total costs	£89	£97	-£8

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

There are no adverse events for UroShield or SoC.

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

None

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

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There are several areas of resource savings that have not been included that UroShield is likely to achieve that have not been included due to lack of direct evidence of impact or to keep the model simple and focused on the immediate impacts of CAUTI:

- The NIHR HTA by Pickard et al showed at least half of catheter associated UTI are likely to occur after a catheter is removed and probably after discharge. Reduction in UTIs that are not hospital onset have not been included in the model.
- Reduction in CAUTI and bacteriuria with UroShield is also likely to reduce catheter blockage and associated costs to rectify, particularly with regard to the reduction of visits to A&E and unplanned hospital admissions.

The Medical Technology Group (MTG) found that the NHS in England spent in 2013/14, £434 million on treating 184,000 emergency admissions caused by a urinary tract infection. This is a per patient cost of £2,361. Referring to Wales, it states that a problem with understanding the extent of the problem of CAUTIs is that currently they are not recorded by Health Boards. It is clear that accurate data capture of the incidence of UTIs, and CAUTIs in particular, is crucial in order to determine the extent of the problem, and the impact of implementing best practice measures within services. The same research also showed that Clinical Commissioning Groups (CCGs) in England spend an average of £84,609 each per year on patients who have been admitted to hospital for a blocked catheter. This equates to 39% of all cases being treated in a hospital setting – unnecessarily costing

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the NHS over £17 million a year (this is if they do not subsequently present with a CAUTI). Continence services in Wales, similar to England, also have to tackle the challenge of blocked catheters. This is a procedure that should be performed safely, cheaply, and routinely in the community or if possibly reduced significantly, with no unnecessary cost to the acute sector.

- The community patient population who experience high rates of infection generally have other complex healthcare needs that are unique and therefore cannot be generalised into a model. The cost of care for these patients should they acquire an infection can be considerably higher.
- Costs of long-term care required for survivors of sepsis has not been included.
- Reduction in need to use antibiotics and repeated use of antibiotics in patients with recurrent CAUTI. This reduces the likelihood of antibiotic resistance developing in an individual as well as antibiotic resistant strains developing in the population.
- By reducing CAUTIs and extended length of stay, UroShield frees up hospital acute and ICU beds which increases capacity in hospitals and reduces the cancellation of operations due to unanticipated demand for acute and ICU beds due to CAUTI.
- Deaths are reduced and associated end of life costs have not been included.

NHS England reported in 2014 that urinary tract infections (UTIs) were the condition with the highest emergency admissions rates (NICE 2018). Of these UTIs, between 43% and 56% were associated with a urinary catheter (Loveday et al 2014). With 10% of residents in care homes and 15-25% of hospital inpatients using a long-term catheter, the likelihood of these patients developing a catheter associated urinary tract infection (CAUTI) is increased considerably. Furthermore urine contamination (bacteriuria) occurs at the rate of 3 to 10% per day with 100% of patients developing asymptomatic bacterial contamination after 30 days of catheterisation. We know that 24% of patients affected by asymptomatic bacteriuria will go onto develop symptoms of a CAUTI (Epic 3). Whilst infrequent, approximately 3.6% of cases with CAUTIs can lead to life threatening conditions, such as bacteraemia or sepsis, where mortality rates range from 10-33%.

Total costs

In the following tables, summarise the total costs: Summarise total costs for the technology in table 7.

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- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	The cost of the driver varies between £3 and £20 per patient in hospital setting. In the community setting the cost of the driver is £15 per month	From model
Consumables per year (if applicable) and over lifetime of device	£50 per patient (if catheterised less than 30 days) or £50 per 30 days	NanoVibronix
Maintenance cost per year and over lifetime of device	£0	Assumption
Training cost over lifetime of device	£0	Assumption
Other costs per year and over lifetime of device	£0	NanoVibronix
Total cost per treatment/patient over lifetime of device	For hospitalised patients, the cost varies per patient between £53 and £120 depending on length of time catheter is in place. For community patients the cost is £65 per month.	From model

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Patients in hospital – all patients catheterised

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£5	£0	+£5
CAUTI	£20	£81	-£61
Consumables	£50	£0	+£50

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Total	£75	£81	-£6

Patients in hospital – patients catheterised<28 days

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£3	£0	+£3
CAUTI	£19	£74	-£55
Consumables	£50	£0	+£50
Total	£72	£74	-£2

Patients in hospital – patients catheterised>28 days

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£20	£0	+£20
CAUTI	£55	£217	-£162
Consumables	£100	£0	+£100
Total	£175	£217	-£42

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Patients in hospital – patients catheterised in ICU

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£5	£0	+£5
CAUTI	£28	£113	-£85
Consumables	£50	£0	+£50
Total	£83	£113	-£29

Patients in community – all patients with indwelling catheter (cost per month)

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£15	£0	+£15
CAUTI	£8	£33	-£25
Consumables	£50	£0	+£50
Total	£73	£33	+£40

Patients in community – patients with recurrent CAUTI (cost per month)

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in mean discounted cost per patient (£): technology vs comparator
Device cost	£15	£0	+£15
CAUTI	£24	£97	-£73
Consumables	£50	£0	+£50
Total	£89	£97	-£8

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Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Scenario 1

The lower rate of CAUTI risk reduction (96% at 3 months with one month of use of UroShield) identified in the study by Markowitz et al was used as the efficacy parameter for UroShield.

Describe the differences between the base case and each scenario analysis.

The scenario analysis assumes greater efficacy for UroShield.

Describe how the scenario analyses were included in the cost analysis.

The efficacy parameter for UroShield was increased to 96% for all patient groups considered in the analysis.

Describe the evidence that justifies including any scenario analyses.

As the Markowitz study is explicitly on infections and the only RCT evidence available for this scenario reflects the efficacy that NanoVibronix considers UroShield would have in the real world more so than the meta-analysis estimate used in the base case.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£)*
Scenario 1			
Hospital - All	£58	£81	-£22.97
Hospital <28 days	£56	£74	-£17.24
Hospital >28 days	£129	£217	-£88.00
ICU	£59	£113	-£53.37

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Community – All (per month)	£66	£33	£32.99
Community – Recurrent (per month)	£68	£97	-£28.27

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

One way deterministic sensitivity analysis was performed across the range of values for each parameter provided in Table 3

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

See Table 3. The values chosen were either derived directly from the source for the base case value or where this was not available or the value was based upon assumption the base case value was increased/decreased by 25%.

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All parameters in table 3 were varied

Sensitivity analyses results

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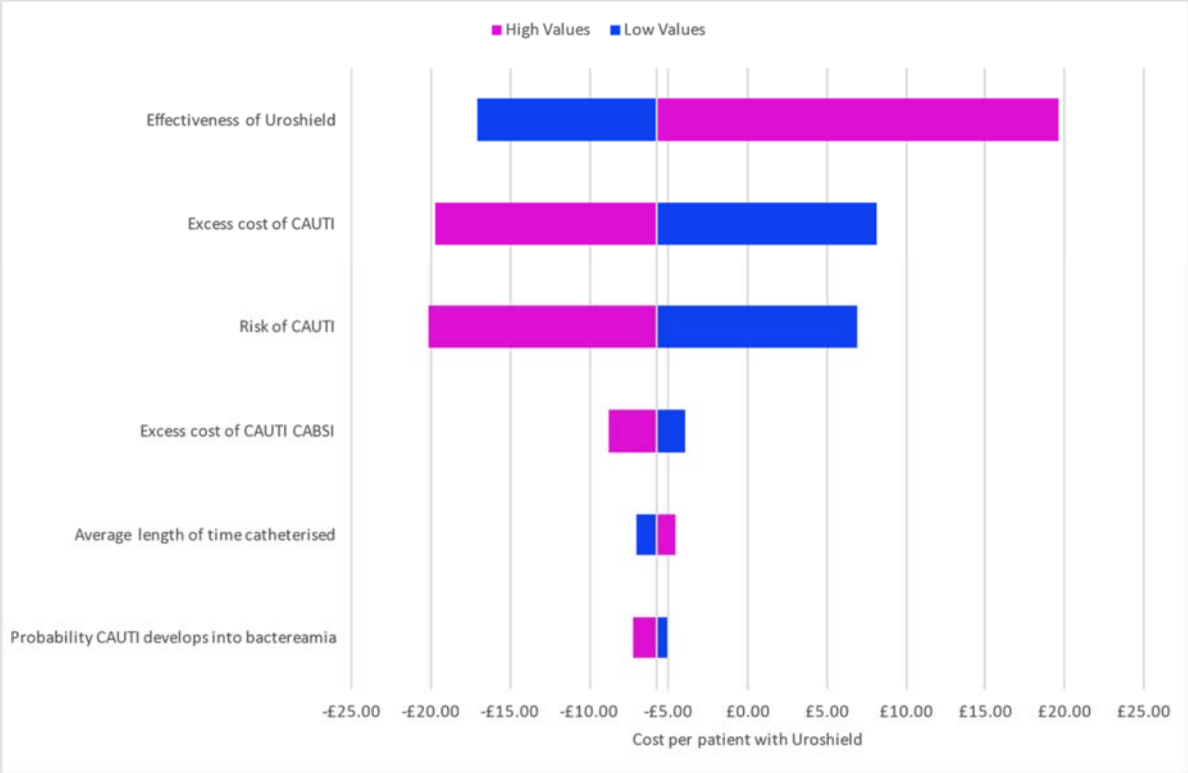
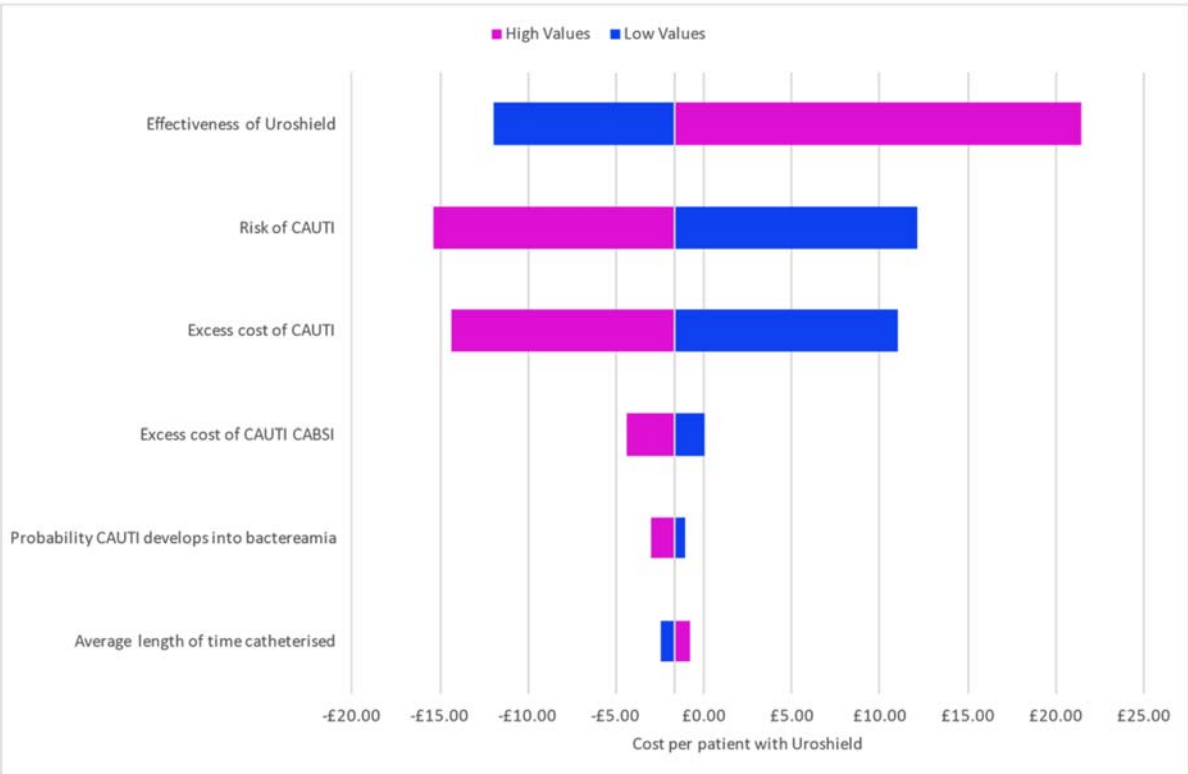
Hospital – all patients



Hospital <28 days



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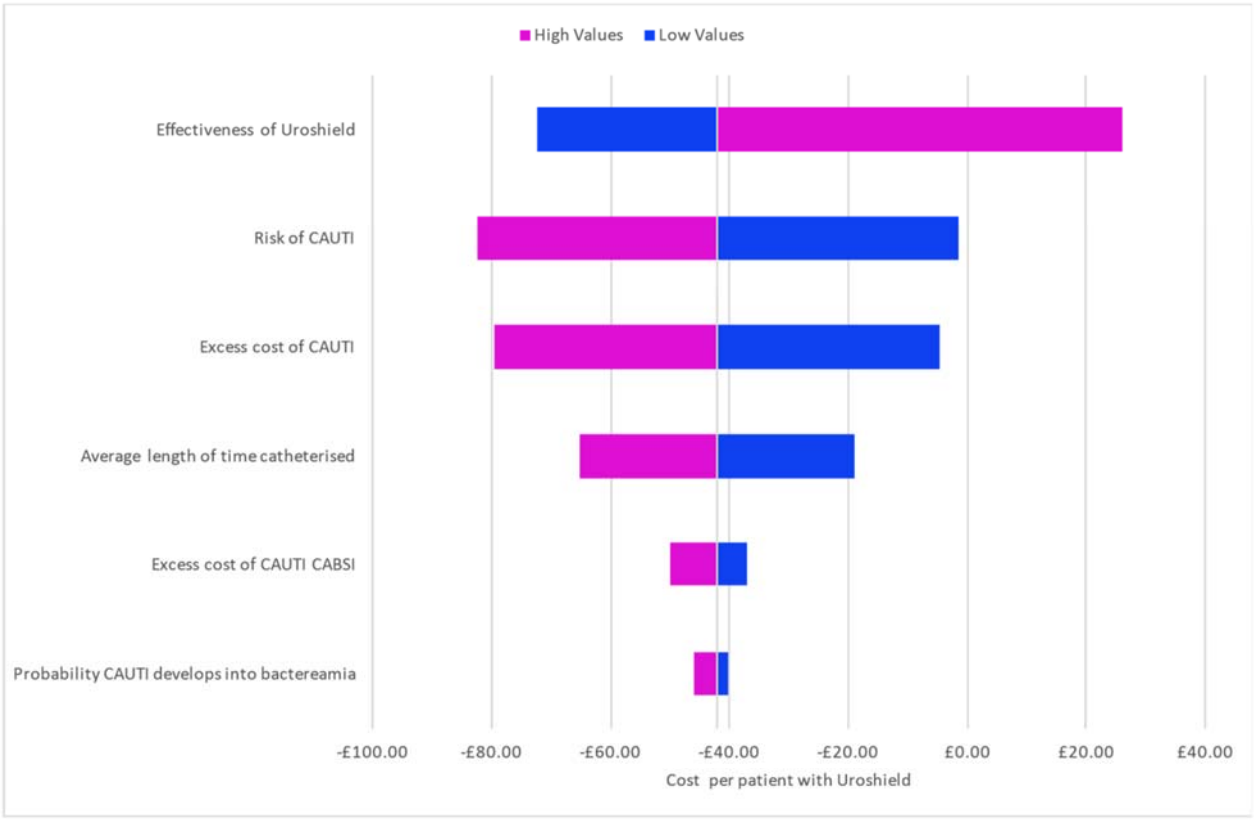
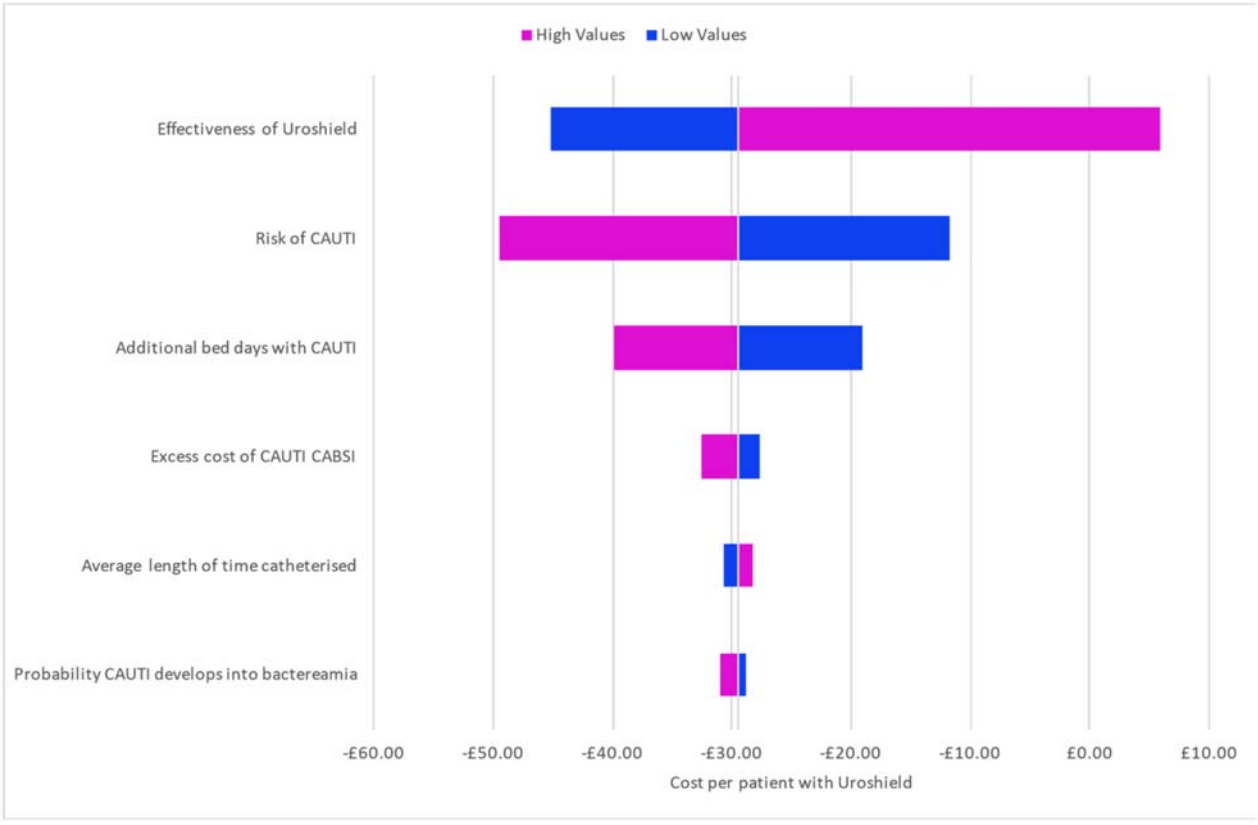
Hospital >28 days



Hospital - ICU



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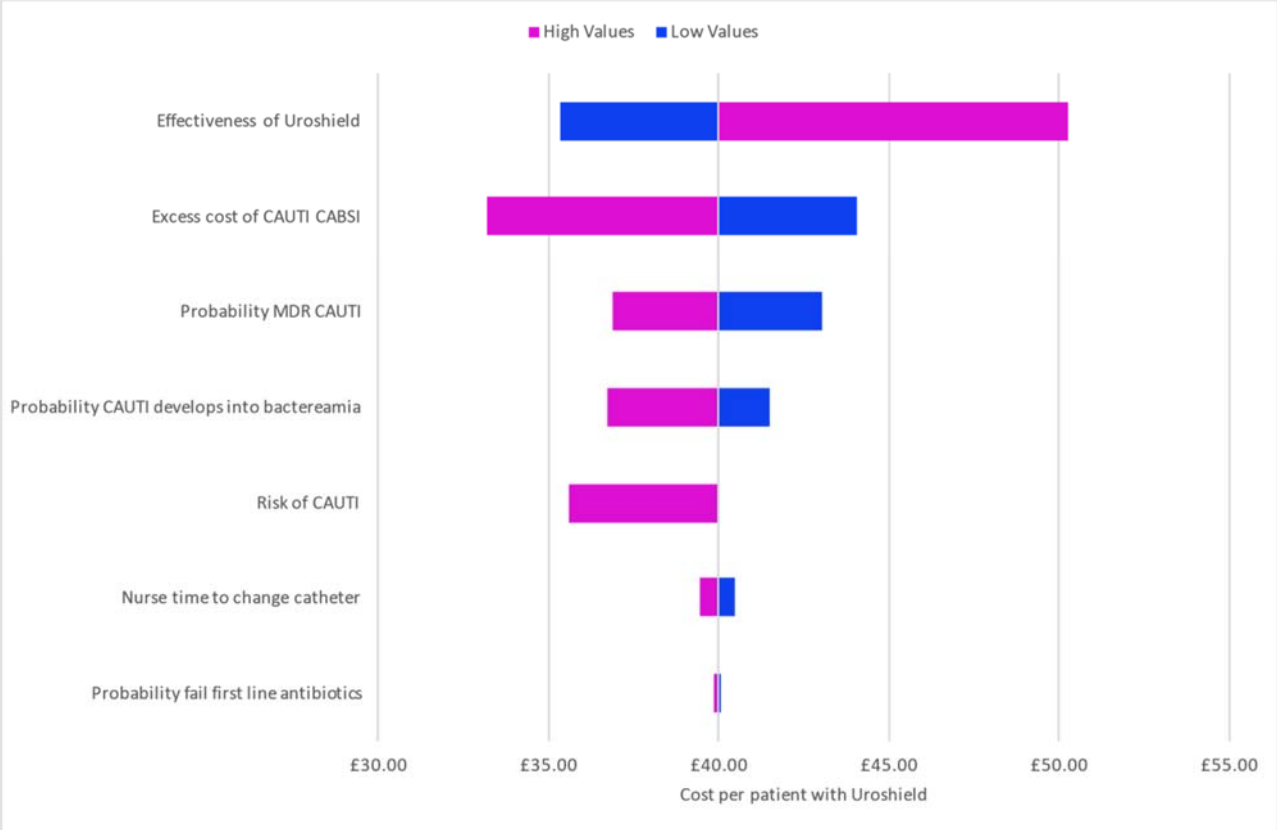
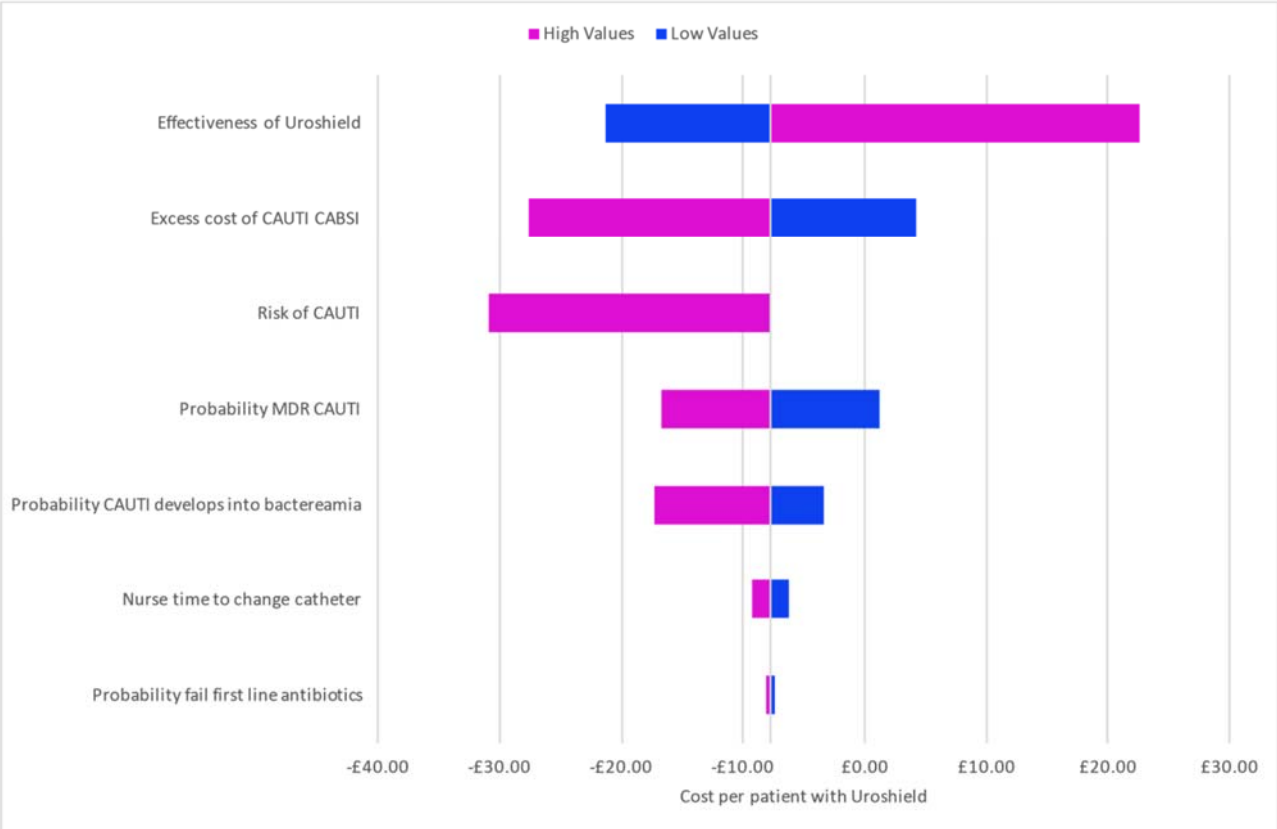
Community – All



Community – Recurrent



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What were the main findings of each of the sensitivity analyses?

For all settings, the single most important area of uncertainty is the effectiveness of UroShield. In hospital settings, results were also sensitive to the risk of CAUTI and the excess cost of CAUTI. Results were insensitive to CABSI rates or costs. In community settings however results are sensitive to CABSI costs as these are a greater proportion of the potential savings in the community setting than the hospital setting.

What are the main sources of uncertainty about the model's conclusions?

The efficacy of UroShield in all settings at stopping CAUTI is somewhat uncertain, although the rates used in the model from the meta-analysis compared to those from the most robust studies would indicate that the model has underestimated efficacy rather than overestimated efficacy. Risk of CAUTI is also important in the hospital setting but only in all patients and those with catheterisation <28 days.

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Miscellaneous results

Include any other relevant results here.

Though not included in the cost analysis, by preventing CAUTI and therefore blood stream infections and death, UroShield will save lives. In the base case analysis, the number needed to treat to prevent one death was calculated for each patient group considered and is presented below

Patient group	NNT with UroShield to prevent one death from CABSI
Hospital - All	3,759
Hospital <28 days	4,140
Hospital >28 days	1,404
ICU	3,759
Community - All	1,680
Community - Recurrent	571

In addition, each CAUTI has a QALY loss, which in Pickard et al was estimated to be 0.006 (excluding any loss of life from CABSI). Whilst this is a small loss overall, if valued at £20,000 a QALY, each CAUTI avoided generate £120 in patient benefit.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

As a simple decision tree, the model parameters and algorithms were able to be checked internally. There are no external evidence sources outside of those used within the model to validate the model outputs.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Clinical experts were asked to validate the assumptions in the model. The clinicians approach considered the assumptions to be reasonable but felt unable to confirm the assumptions around the average length of time people are catheterised and that UroShield would be equally effective in all settings due to the variability inherent in length of catheterisation and their lack of technical knowledge on the UroShield device.

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4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The cost model provides evidence that for all patients catheterised in hospital (including patients with short term (<28 days) and long term (>28 days) catheterisation and those in ICU) UroShield would be cost saving through reduction in development of CAUTIs. In the community setting, the cost model suggests that UroShield would not be cost-saving for all patients as the rate of CAUTI in all patients with a long term indwelling catheter are too low. However, for patients with at least two CAUTIs a year ('recurrent CAUTI') UroShield would be cost saving.

The savings seen occur in the base case even when pessimistic values for the efficacy of UroShield and other conservative values are used in the model.

Briefly discuss the relevance of the evidence base to the scope.

The rates of CAUTI and costs are taken directly from sources that were derived specifically from the NHS and for patient populations in the scope (with the exception of ICU). The efficacy of UroShield was taken from studies in multiple settings and has been assumed to be the same regardless of setting or population.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

There are no published economic studies on UroShield.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

As the CAUTI rates are taken directly from a large, recent study of patients in the acute setting in England and the community rates are similarly either predefined (for recurrent patients) or from an English survey (for all patients), the CAUTI rates used in the model are relevant to all patient groups in the scope. Costs have been sourced from reference costs, the BNF or models underpinning NICE guidelines and so are directly applicable to NHS settings. Efficacy of UroShield was assumed to be the same regardless of setting in which it is used.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths

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The model is simple, with minimal assumptions and designed to focus on the benefits of UroShield from stopping CAUTI. CAUTI rates are sourced from robust sources that are directly relevant to the English NHS. The majority of costs in the model are from robust sources. The base case model took a number of conservative assumptions that would underestimate the cost-effectiveness of UroShield. The model results were largely insensitive across the range of parameter values considered in the sensitivity analysis.

Weaknesses

The efficacy of UroShield is based upon a small number of relatively small trials and effectiveness across all settings was assumed to be equivalent. The cost of hospital onset CAUTI is uncertain, although a conservative approach was adopted in selecting a value that is likely lower than the actual value.

Detail any further analyses that could be done to improve the reliability of the results.

An ongoing independent single-arm trial is being undertaken in a community setting in Southampton which will add to the evidence base on UroShield efficacy. NanoVibronix consider that whilst the current evidence base is limited to a small number of studies, although supported by the underlying evidence on how UroShield limits bacterial growth and reduces CAUTI, a full RCT in an NHS hospital setting would provide gold standard evidence on the effectiveness of Uroshield in acute patients.

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5 References

Please include all references below using NICE's standard referencing style.

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6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	14/06/2021
Date span of search:	2000-2021

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Search strings were drawn from the following phrases or words:

Population – Urinary catheter, long term, indwelling urinary catheter,

Intervention – Uroshield, ultrasonic waves, acoustic shield, Nanovibronix,

Comparator – standard of care

Outcomes – bacteriuria, CFU, bacterial counts, colonis(z)ation, biofilm, infection , UTI, CAUTI, pain, spasm, discomfort, quality of life, cost effectiveness or cost benefit analysis, economic modelling, healthcare resource use

Limits: 2000-2021, English

Search strategies and results are shown below

Published studies

Date	Database	Terms	Results
14/06/2021	Medline	((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND ((exp *"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab) AND ((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp "URINARY TRACT INFECTIONS"/ OR exp BACTERIURIA/ OR (bacter* CFU).ti,ab OR (bacterial colonisation OR bacterial colonization).ti,ab OR (biofilm).ti,ab OR (CAUTI).ti,ab OR (pain OR spasm OR discomfort).ti,ab OR (quality of life).ti,ab)))) [DT 2000-2021] [Languages English]	67 results
14/06/2021	Medline	((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND ((exp	0 (zero)

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		*"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab) AND ((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp "URINARY TRACT INFECTIONS"/ OR exp BACTERIURIA/ OR (bacter* CFU).ti,ab OR (bacterial colonisation OR bacterial colonization).ti,ab OR (biofilm).ti,ab OR (CAUTI).ti,ab OR (pain OR spasm OR discomfort).ti,ab OR (quality of life).ti,ab)))) AND (exp ULTRASONICS/ OR (uroshield OR NanoVibronix).ti,ab OR (acoustic shield OR surface acoustic waves).ti,ab)	results
14/06/2021	PubMed	((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND ((COSTS AND COST ANALYSIS).ti,ab OR (ECONOMIC MODELS).ti,ab OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR costefficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab)) AND ((((urinary catheter* OR foley catheter* OR urethral catheter* OR ureteral catheter*).ti,ab OR (urinary catheter OR foley catheter OR urethral catheter OR ureteral catheter).ti,ab OR (urinary catheterization OR foley catheterization OR urethral catheterization OR ureteral catheterization).ti,ab) AND (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life).ti,ab) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation))	92 results

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14/06/2021	PubMed	((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND ((COSTS AND COST ANALYSIS).ti,ab OR (ECONOMIC MODELS).ti,ab OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR costefficiency OR cost minimisation OR budget impact OR cost	0 (zero) results
		effectiveness).ti,ab)) AND ((((urinary catheter* OR foley catheter* OR urethral catheter* OR ureteral catheter*).ti,ab OR (urinary catheter OR foley catheter OR urethral catheter OR ureteral catheter).ti,ab OR (urinary catheterization OR foley catheterization OR urethral catheterization OR ureteral catheterization).ti,ab) AND (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life).ti,ab) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation)) AND (NanoVibronix OR uroshield).ti,ab	
14/06/2021	Embase	(((exp "URINARY TRACT INFECTION"/ OR (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life OR adverse events).ti,ab) AND ((exp "UROLOGICAL CATHETER"/ OR exp "URINARY CATHETER"/ OR (long term urinary catheter).ti,ab OR exp "BLADDER CATHETERIZATION"/ OR (indwelling urinary catheter).ti,ab) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).ti,ab)) AND ((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND (exp *"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab OR exp *"HEALTH CARE COST"/))) [DT 2000-2021] [English language]	57 results

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14/06/2021	Embase	((uroshield OR NanoVibronix).ti,ab AND (((exp "URINARY TRACT INFECTION"/ OR (bacteriuria OR bacter* cfu OR bacterial colonisation OR bacterial colonization OR biofilm OR CAUTI OR pain OR spasm OR discomfort OR quality of life OR adverse events).ti,ab) AND ((exp "UROLOGICAL CATHETER"/ OR exp "URINARY CATHETER"/ OR (long term urinary catheter).ti,ab OR exp "BLADDER CATHETERIZATION"/ OR (indwelling urinary catheter).ti,ab) AND (clinical OR clinical trial OR randomised controlled trial OR randomized control trial OR clinical study OR clinical evaluation).ti,ab)) AND ((evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab AND (exp *"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab OR exp *"HEALTH CARE COST"/)))) [DT 2000-2021] [English language]	0 (zero) results
14/06/2021	Cinahl	(((exp *"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab OR exp *"HEALTH CARE COST"/) AND (evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab) AND (exp "CATHETERS, URINARY"/ OR exp "URINARY CATHETERIZATION"/ OR indwelling urinary catheter OR long term urinary catheter)) [DT 2000-2021] [Languages eng]	54 results

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14/06/2021	Cinahl	((((exp *"COSTS AND COST ANALYSIS"/ OR exp *"MODELS, ECONOMIC"/ OR (Markov).ti,ab OR (incremental cost-effectiveness ratio OR ICER).ti,ab OR (economic OR cost benefit OR cost-utility OR cost-efficiency OR cost minimisation OR budget impact OR cost effectiveness).ti,ab OR exp *"HEALTH CARE COST"/) AND (evaluation* OR analys* OR model* OR simulation* OR assessment*).ti,ab) AND (exp "CATHETERS, URINARY"/ OR exp "URINARY CATHETERIZATION"/ OR indwelling urinary catheter OR long term urinary catheter)) AND (NanoVibronix OR uroshield).ti,ab) [DT 20002021] [Languages eng]	0 (zero) results

Additional search strategies for CAUTI rates were undertaken using the following search terms in Medline, Pubmed and Embase

((incidence* OR prevalence* OR rate).ti,ab AND ((exp "URINARY CATHETERS"/ OR exp "URINARY CATHETERIZATION"/ OR (long term urinary catheter).ti,ab OR (indwelling urinary catheter).ti,ab) AND (exp "URINARY TRACT INFECTIONS"/ OR exp BACTERIURIA/ OR (bacter* CFU).ti,ab OR (bacterial colonisation OR bacterial colonization).ti,ab OR (biofilm).ti,ab OR (CAUTI).ti,ab OR (pain OR spasm OR discomfort).ti,ab OR (quality of life).ti,ab)))) [DT 2000-2021] [Languages English]

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

None

Inclusion and exclusion criteria:

Inclusion – use of Uroshield in relevant patient population (catheterised patients), health economic or other healthcare resource data

Exclusion – use of non-Uroshield devices, use of ultrasound for imaging, histotripsy, non-human studies including in vitro laboratory studies, no healthcare resource data

Data abstraction strategy:

Double data extraction with any conflicts resolved by a third reviewer

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Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Studies identified by searches: 270

Studies excluded as irrelevant at abstract sifting: 270

Studies included at full text review:0

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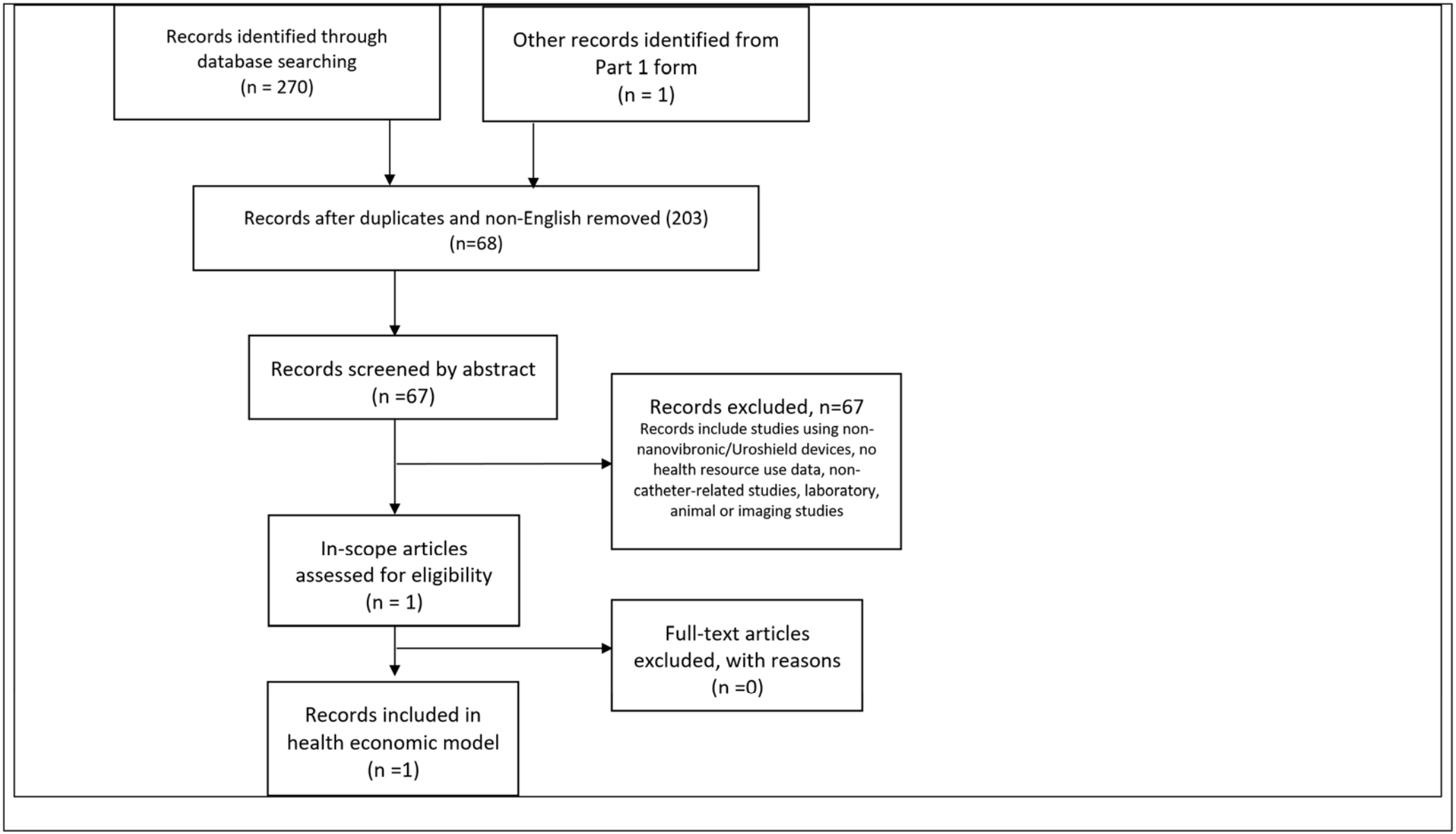

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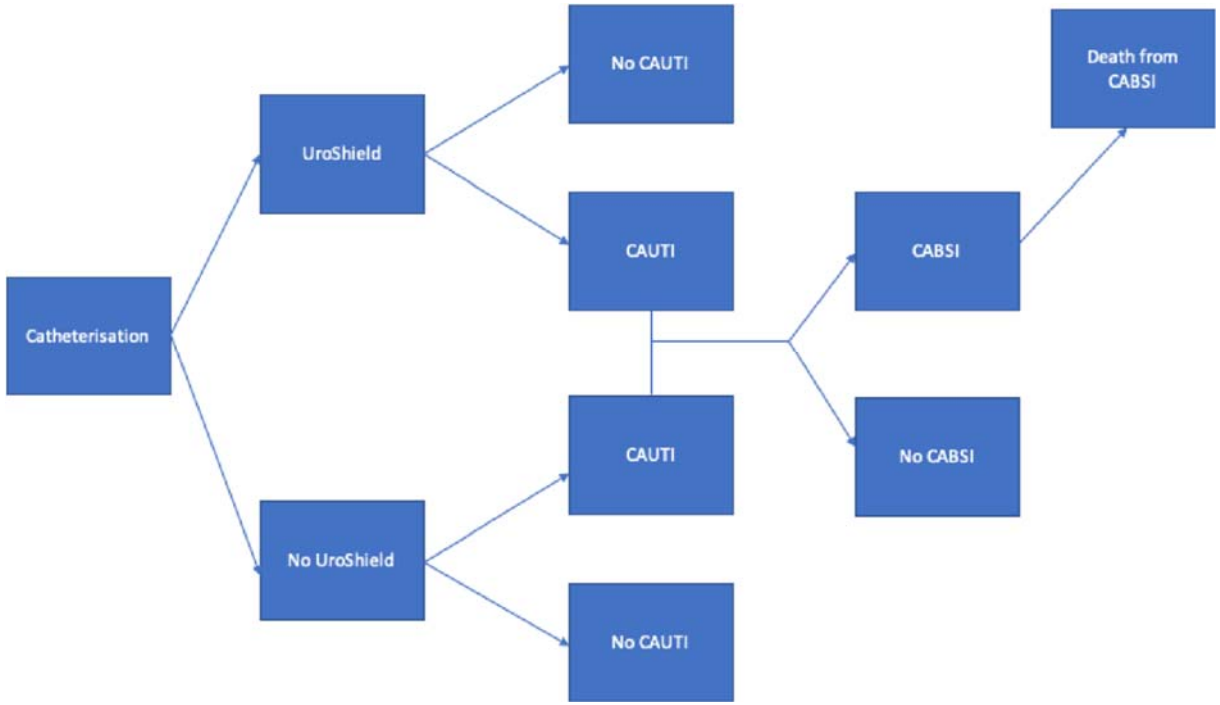
Appendix B: Model structure

Hospital patients



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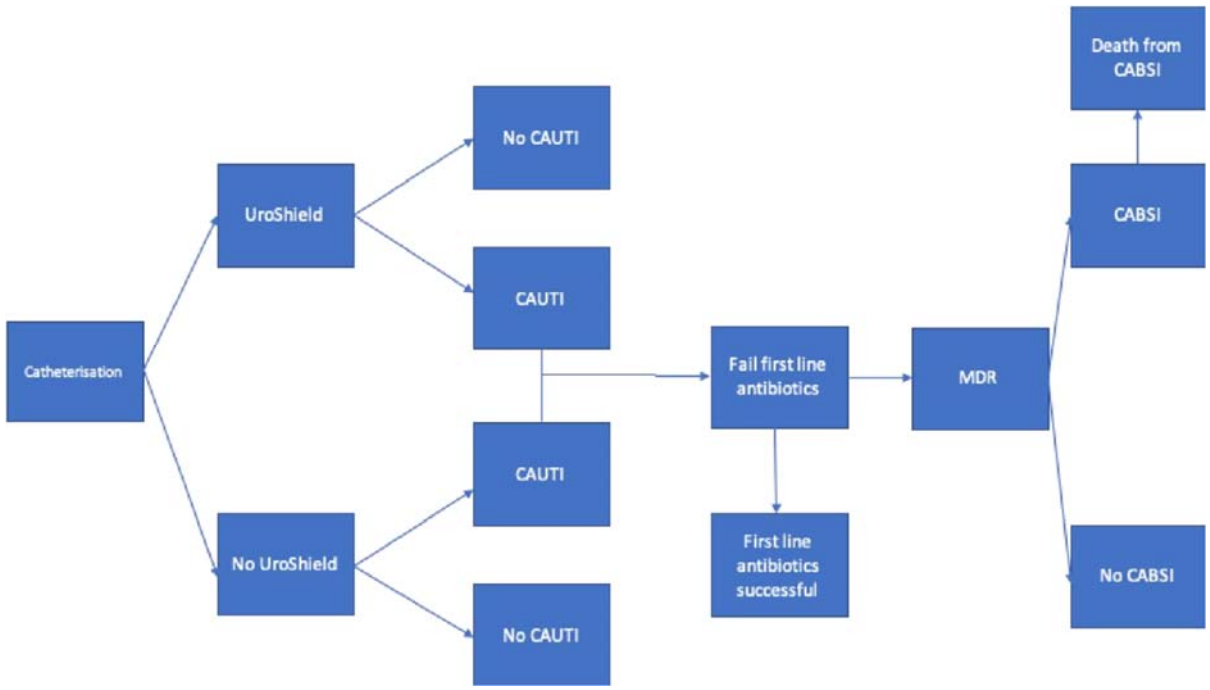
Community patients



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Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No X If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submiof evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. ssion Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page #	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
		Enter text.	Enter text.
	☐ Commercial in confidence		
	☐ Academic in confidence		
Details	Enter text.		
#		Enter text.	Enter text.
	☐ Commercial in confidence		
	☐ Academic in confidence		
Details	Enter text.		

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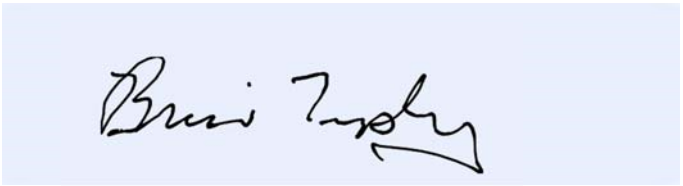
Confidential information declaration I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: Date:

** Must be Medical Director or equivalent*



Click or tap here to enter text 6/25/21

Print: Click or tap here to enter text Brian Murphy **Role /** CEO

Click or tap here to enter text. **organisation:** Nanovibronix Inc

Contact email: Click or tap here to enter text.

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National Institute for Health and Care Excellence

Collated expert questionnaires

MTG Medtech Guidance: UroShield for preventing catheter-associated urinary tract infections

Expert and declarations of interest:

Expert #1	Jane Miles, Urology Nurse Specialist for Benign Disease, Frimley Health Foundation Trust
	DOI: None
Expert #2	Ann Yates, Director of Continence Services, Cardiff and Vale University Health Board
	DOI: None
Expert #3	Mustafa Hilmy, Consultant Urological Surgeon, York Teaching Hospital
	DOI: None
Expert #4	Marcus Drake, Prof of Physiological Urology, Univ of Bristol
	DOI: None
Expert #5	Catriona Anderson, Portfolio GP (special interest in women's health and urogynae infections), Focus Medical Clinic
	DOI: Provided consultancy work for Mylan around the urinary antiseptic Hiprex
Expert #6	Elaine Sutcliffe, Continence Team Leader, Hereford and Worcestershire Health and Care NHS Trust
	DOI: None
Expert #7	Sheilagh Reid, Consultant urological surgeon, Sheffield Teaching Hospital
	DOI: None
Expert #8	Claire Fairbrother, Continence Nurse Prescribing Advisor, NHFT
	DOI: None

	Questions	
1	Please describe your level of experience with the procedure/technology, for example: − Are you familiar with the procedure/technology? − Have you used it or are you currently using it? − Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Expert #1 I have been using the device since April 2018 trialling the technology on a total of 12 patients, and am continuing to trial, I have not been involved in any research or development of the product but was asked to speak at the February Infection Prevention conference in London, on the impact it has had on some of my patients. I was paid to attend this meeting. I am hoping to be involved in some research in the future with I believe Southampton University in collecting catheter samples prior to the start of using the device and at the end of 3 months, in order that the microbiologists will be able to determine the amount of colonisation prior to and post use of the product as well as the type of bacterial infestation. Although several hospitals have trialled the product, I do not believe it is yet widely used within the NHS.
		Expert #2 I am not familiar with the technology or had any experience in its use. I have not been involved with any research projects or audits with regards to this technology and am unaware of it being used in the UHB I currently work for or any where in Wales. The only places that have said they have tried using the device are the ones contained in the information that was sent to me by yourselves. I do not believe it is currently being used widely within the NHS
		Expert #3 No to all
		Expert #4 I am familiar with it. I have not used it. I have no involvement in its development, or subsequent research. I don't know how widely it is used.
		Expert #5 Although very familiar with catherisation procedures and experience of managing patients with long term catheters, both urethral and suprapubic, I have not yet had any hands-on experience with the novel Uroshield device. However, having read about the technology involved in Uroshield,

		and with an in-depth background knowledge of microbiology and biofilm science I have a good understanding of the mechanism by which this technology improves healthcare outcomes. I have not personally had experience of using Uroshield yet with any catheterised patients. I am aware that this technology is currently not widely used in the NHS and the speed of uptake is generally slow. This technology is not currently being used in medical specialities other than those addressing urology and complex UTI.
		Expert #6 Our team were introduced to this device 3 years ago and took it to our Trust's Director of Nursing and microbiology team. It was decided we would complete a 12 week evaluation regarding its effectiveness in reducing infections and catheter blockage. This is now complete. During this evaluation I met with patients to set them up with the device and evaluate its effectiveness. I helped create the evaluation documentation. Myself and my team have previously used the device as detailed above. The evaluation was only for 3 months We chose patients known to our community nursing teams and Acute Trust urology teams who were having ongoing catheter problems and infections that had not responded to other treatments. Some patients were reluctant to try the device as they did not want to be part of a trial or did not want to be connected to it for 24 hours a day.
		Expert #7 I am a consultant urological surgeon of 13 years experiences attached to the spinal injuries unit in Sheffield. I specialise in neurourology and therefore have a wealth of experience managing patients with long term catheters. I am also the chair of the FNUU (female neurourology and urodynamics) section of BAUS (british association of urological surgeons). We have recently produced a consensus document along with the BAUN (british association of urological nurse) on the 'Management of Complications of Long Term Catheters'. This has just been accepted for publication by the BJUI s should be available soon and I suggest you use it in your review looking at options for managing these complications.

		I am familiar with this technology only in terms of the research I have done on it for the paper but I am very familiar with the sort of problems catheterised patients have I am not aware of anyone using this although they may be. I suspect it will not have a quick uptake I think if it is used it should be directed by urologists as part of the armamentarium for CAUTI and catheter blockages
		Expert #8 I have initiated a Uroshield device with one patient who has continued to use this independently and funded by the company. The patient has a complex medical history and was very keen to try the device and feels they have had a positive experience with it. Another member of my team also trialled the device with a patient but this was not successful as there was not a clear plan, patient could not manage the device and had a diagnosis of MS which the trial was then withdrawn for. I think currently the technology use is restricted by access to funding so there is a limited number of patients using it. There are also other limiting factors such as needing a degree of independence and dexterity to be able to manage the device, charging time that the device needs and wearability.
2	Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert # 4 – not asked
		Expert #5 I have done bibliographic research on this procedure.
		Expert #6 I have done bibliographic research on this procedure.

		Expert #7 I have done bibliographic research on this procedure. As above regarding the consensus document
		Expert #8 I have had no involvement in research on this procedure.
	Has the technology been superseded or replaced? (MIB question)	Expert #1 No
		Expert #2 It is currently the first of its design there is not a device prior to this that has been used so it is not replacing or superseding any other device and as far as I am aware there is nothing that has been developed to replace or supersede this
		Expert #3 no
		Expert #4 No
		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked
		Expert #8 – not asked

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design?	Expert #1 This is a huge improvement where current standard is to use regular bladder maintenance solutions to reduce blockages, with catheters being changed more frequently than the usual 10-12 weeks. I feel this is a novel concept/design and in the 23 years I have been in post have found it to be the first thing that works in reducing blockages and catheter changes.
		Expert #2 It is an innovative device compared to current standard care which usually looks at Aseptic insertion / care of indwelling catheters, best evidence practice in line with national guidance NICE/ EPIC/ EAUN. There are other devices which claim to assist with UTI's in indwelling catheters i.e. Farco Fill, Polyhexanide. Which are either instilled in catheter balloon or directly into bladder. However this is the first device of its kind developed to be fitted externally
		Expert #3 Novel concept
		Expert #4 Novel, potentially valuable
		Expert #5 This is a very innovative approach to a major problem which in universally acknowledged to effect patient care where extended catheterisation is a necessity.
		Expert #6 It is a novel and exciting new design for an area of care which requires new innovation. There is current suggested treatment for catheter blockage and urine infections but to have a new non invasive device for those who do not respond to standard treatment is welcomed.
		Expert #7 Very innovative and interesting although I am not sure how practical it will be

		Expert #8 The device feels like a big innovation in terms of catheter care and UTI prevention which is a huge problem as is antibiotic resistance and a new tool to help reduce this would be of great benefit.
	Which of the following best describes the procedure (please choose one):	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 The first in a new class of procedure.
		Expert #6 The first in a new class of procedure.
		Expert #7 Definitely novel and of uncertain safety and efficacy.
		Expert #8 Definitely novel and of uncertain safety and efficacy The first in a new class of procedure.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1 It would not replace the current standard of care as mention in section 14. But would be useful to have this product available for all patients where other interventions have failed.
		Expert #2 No it would be required as well as current best practice

		Expert #3 Addition
		Expert #4 Addition
		Expert #5 Addition to existing standard care
		Expert #6 As an addition to existing care
		Expert #7 Used in addition
		Expert #8 Addition to standard care

Current management

5	Please describe the current standard of care that is used in the NHS.	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 The current best practice within the NHS adheres to following the guidelines to reduce infection risk. This is achieved via good clinical practice around insertion and catheter maintenance, in addition to removal of catheter at earliest appropriate opportunity.
		Expert #6 Catheters, antibiotics, catheter care, catheter valve
		Expert #7 Assuming this is to be used to decrease the risk of CAUTI and catheter blockage then the standard of care is good nursing care , catheter changes as needed and antibiotics only for symptomatic problems. There is a difference in those that have long term and short term catheters and I struggle to see how this can used for long term catheter if it need to be clipped on consistently it will be another thing for patients to have to carry around. However I could see a role for those that were really struggling such as the very disabled with minimal mobility significant CAUTI impairing quality of life
		Expert #8 Standard hygiene measures for catheter care, fluid intake, good bowel care, use of antibiotics if symptomatic of UTI. I personally feel that there is still work to be done to improve basic catheter care.
6	Are you aware of any other competing or alternative procedure/technology available	Expert #1 No

	to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #2 I am not aware of any devices which have an action like this as it is a unique device but have already suggested above devices / care that also claim to reduce UTI's in indwelling catheters
		Expert #3 No
		Expert #4 No
		Expert #5 There are various novel coated catheters whose objective is to reduce bacterial adhesion and biofilm formation, however, unfortunately the evidence thus far has not demonstrated great efficacy.
		Expert #6 No
		Expert #7 No
		Expert #8 There is no other device using ultrasonic technology like this that I am aware of.

Potential patient benefits

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1 Reduced blockages and infections, resulting in better quality of life, one of my patients with a high spinal injury has had a reduction in symptomatic UTI's which have in the past needed hospitalisation to treat and has also found that her bowel management is much easier as she has less bladder/bowel spasm

		Expert #2 If there is a reduction in bacteria adhering to the catheter and causing bio films then the reduction in UTI's could be a great benefit. Patient would require less antibiotics, reduce risk of antimicrobial resistance, less pain and discomfort and potentially less visits to Acute settings. It could also reduce the risk of E Coli which is now a recordable bacteria target for the NHS
		Expert #3 Reducing CAUTI
		Expert #4 Reduced encrustation, lower chance of blockage, perhaps reduced infections
		Expert #5 Reducing infection risks
		Expert #6 Non invasive, external device which can reduce number of catheter changes and prevent urinary tract infections. Most of the patients who completed the evaluation say this device has changed their lives. It has prevented infections and associated symptoms that come with this. It will not necessarily be a first line treatment and so not used on a large number of patients but for those it will be used on are likely to have exhausted all other treatments and make a big difference to their quality of life.
		Expert #7 Decrease CAUTI and catheter blockage
		Expert #8 Reduction in UTI/recurrent UTI. Self-management
8		Expert #1

	Are there any groups of patients who would particularly benefit from using this procedure/technology?	In my experience I have found that patients with MS have found it particularly useful, and I would say those patients who are constantly having blockages where other management options have failed.
		Expert #2 Potentially people who have repeated UTI's due to indwelling catheters and those who may have auto immune suppression i.e. MS patients or any one with neuropathies
		Expert #3 Patient with long-term urethral catheters and suffer from recurrent CAUTIs
		Expert #4 Appears relevant to all catheterised patients
		Expert #5 Long term catheterised patients, immunocompromised patients, patients with anatomical abnormalities of the urinary tract
		Expert #6 Catheterised patients and particularly non mobile ones due to the fact the clip and device need to stay in place for 24 hours a day. Catheterised patients who have blockage and urine infections when all other treatments have failed
		Expert #7 As above
		Expert #8 Spinal injured patients, long term conditions

Potential system impact

9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1 Most certainly, the majority of patients who have used this under my care, have had less visits to either the hospital or by the district nurses, with also a reduction in urinary tract infections
		Expert #2 Potentially yes but I would like the company to address the issues raised earlier as I feel there is a lack of substantial evidence
		Expert #3 Reduce recurrent CAUTIs , which normally lead to course of antibiotic , catheter change and possible hospital admission and serious sepsis
		Expert #4 Lower levels of infection or blockage would reduce primary care demands, and improve quality of life
		Expert #5 Absolutely, the cost of hospital admission in terms of financial, social, physical and psychological costs is significant through the impact of urinary tract infection. This technology has the potential to improve health care outcomes and further studies are awaited to validate the small amount of data already available.
		Expert #6 Yes. Improved quality of life Less invasive care – ie fewer recatheterisations Reduced unscheduled community visits and hospital attendance Fewer antibiotics prescribed

		Expert #7 possible
		Expert #8 I believe so yes. There is potential for reduction in antibiotic use, fewer catheter changes, blocks etc and fewer hospital visits.
	What do you consider to be the potential benefits to the health or care system from using this technology? (MIB question)	Expert #1 I believe that there would be a long term cost saving due to reduced use of antibiotics, fewer hospital admissions and fewer visits by community staff having to either unblock or change catheters
		Expert #2 Lower rates of E Coli/ bacteria adhersion, less emergency admissions due to CAUTI's, potential savings due to both of these
		Expert #3 Reduce antibiotic, and hospital admission
		Expert #4 As 7
		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked
		Expert #8 – not asked
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology	Expert #1 From the investigations we have made in our trust, there would be a cost saving for some patients with just over half of the patients having a cost neutral impact.

	likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #2 it stands there may be very little cost improvement based on the studies undertaken I would prefer further studies undertaken with NHS UK whereby current guidance is being implemented and proper costings undertaken with regards to overall care
		Expert #3 It would cost more, as per the information provided, it would cost £1200. Current practice for long-term catheter to be changed every 12 weeks (catheter cost £8-£10) or more frequently if patient has CAUTIs. Or using the Silver coated catheter (cost around £11) that get changed every 4 weeks.
		Expert #4 Entirely dependent on the actual achieved reductions in blockages or infections
		Expert #5 Although the technology may appear more expensive than traditional catheter costs, when the costs of UTI complications are taken into account, including social and healthcare costs (both primary care, secondary care and community care), this technology could result in overall budget savings.
		Expert #6 Less
		Expert #7 It depend if it works …if my maths is correct it will cost £498 for the driver and a further £80 per 30 days of use, if that were to prevent one hospital admission with CAUTI I suspect it would be worth it
		Expert #8 In terms of community management the device will have a cost increase from standard care but will improve costs in terms of unplanned visits, antibiotic use and potential hospital admission.

11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1 There would hopefully be a shift from the number of patients needing to be hospitalised, but also reducing community nurse time, with fewer visits to administer maintenance solutions or change blocked catheters
		Expert #2 At present I do not believe the relevant evidence is available to be able to make any recommendations
		Expert #3 Simple method
		Expert #4 This may increase demands on care staff, in terms of fitting the device and trouble-shooting any non-function issues
		Expert #5 Although capital expenditure on equipment and maintenance would increase initially, further on costs incurred through infection related health care complications might be avoided which ultimately would be far more expensive than the initial capital outlay. There is a need to not regard the expenditure in isolation, silo budgeting.
		Expert #6 In the community if it was not available on FP10 then the initial set up costs and ongoing costs will have an impact. Also if the device will be used for single patient use or whether there will be a process for them to be returned, cleaned and reused. All this calculated, I still feel it will it will cost less than existing care and more importantly improve peoples quality of life
		Expert #7 As above

		Expert #8 Likely to cost more than good standard care.
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1 None that I can think of, the product is very easy to use, and my patients and their families have been able to remove and replace the device and attach the battery charger with out difficulty
		Expert #2 Yes there would be training required to implement technology and this would have to be across the NHS and private sector for all professionals to be aware of device and use Current e learning programme and training programme would have to be revised
		Expert #3 Minor
		Expert #4 Likely to require simple training for all staff involved
		Expert #5 This technology is straightforward, small, discrete and suitable for near patient experience once instructed by a HCP, primary/ community care would be well suited to instruct and apply this technology.
		Expert #6 Process for the item to be loaned i.e., allocated, delivered, returned, cleaned
		Expert #7 Staff and patients would need to be shown how to use it but I suspect that isn't very difficult. My issue would be around its use in disabled those with long term catheters having to lug around the device, it would need to work very well to make it worth it

		Expert #8 Training for staff, patients and carers. Funding and a process for selection for patients for the devices. Safe storage. A system for repair/service and return or monitoring.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 Yes, but only clear basic training
		Expert #6 Yes for staff and the patient but it is not difficult to use and can be managed with the information provided by the company
		Expert #7 I doubt it
		Expert #8 Yes, staff, patients, families and carers will need training on safe use, storage and monitoring of the equipment. Staff will need to be trained on appropriate selection of patients.

Other considerations

14	What are the potential harms of the procedure/technology?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked

	Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #4 – not asked
		Expert #5 There do not appear to be any harms directly associated with using the device. The ultrasonic vibrations are at a frequency which are undetectable as long as the device is set up correctly. Obviously as the device needs to be charged occasionally safety around the use of a power source and use of/ care for a battery need to adhered to, the device itself should also be kept away from water (shower/ baths)
		Expert #6 Possibly pregnancy safe to use with somebody with a pacemaker No known side effects of use
		Expert #7 The literature states that it is only for use with urethral catheters which is a pity because its use with SPC would mitigate and urethral issues I would have concerns about long term acoustic waves in the urethra, I have not looked into this in any detail but some research would need to be done that continuous stimulation would NOT increase risk of stricture , malignancy or effect the erectile mechanism. I would have particular concerns in tetraplegic patients at risk of dysreflexia that the stimulation might trigger it
		Expert #8 Pressure damage if the device is worn incorrect or not repositioned and the patient has reduced sensation (likelihood may be rare if patient is given education) Device is not effective as not used properly.
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked

		Expert #4 – not asked
		Expert #5 The main key outcome measure would be reduction of catheter associated UTI, other measurable outcomes would; decreased prescribing of antibiotics (enhancing antimicrobial stewardship) reduction in use of scarce health care resources (primary and secondary care), reduced social care burden and increased quality of life for catheter users.
		Expert #6 Improved quality of life Reduced UTI's /Gram negative blood stream infections Reduced use of antibiotics Reduced catheter blockage/problems Reduced unplanned contact with community and acute services
		Expert #7 Decrease CAUTI Decrease catheter blockages and therefore number of catheter changes
		Expert #8 Reduction in occurrence of UTI
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1 no
		Expert #2 As above I would like to know of any contraindications to use if any or any side effects experienced by patients

		Expert #3 Unlikely
		Expert #4 No, but I want to see close follow up to ascertain whether the ultrasound could affect the patient's urethra (leading to stricture, or tissue breakdown in the medium term)
		Expert #5 As with any fairly new technology there may well be unseen problems ahead, however
		Expert #6 Patient compliance as needs to be in place for 24 hours
		Expert #7 As above 14
		Expert #8 Efficacy with Multiple Sclerosis patients-has this been evidenced?
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 The main source of uncertainty around this device circles around the capital expenditure, also key opinion leaders in the field continue to monitor performance in use
		Expert #6 None known

		Expert #7 Not that I am aware of
		Expert #8 Not that I am aware
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 Cannot predict at present.
		Expert #6 Most or all district general hospitals.- yes A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK. Cannot predict at present.
		Expert #7 Cannot predict at present.
		Expert #8 Community based Cannot predict at present.

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1 As mentioned in section 1 I would be happy to share details of locally collected data with NICE
		Expert #2 I am unaware of any further research into this technology
		Expert #3 No
		Expert #4 No
		Expert #5 There is no other published data besides that which a comprehensive would reveal
		Expert #6 Effectiveness of Uroshield on reducing urinary tract infections (UTIs): A Real-World Evaluation Associate Professor, Dr Ksenija Maravic da Silva
		Expert #7 EAU abstract 2011. The other papers I have found on the Uroshield website which I am sure you have seen I couldn't find anything more
		Expert #8 (no response)
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1 None

		Expert #2 No but would recommend that there is some more evidence especially within a UK health setting
		Expert #3 More information on the company website and a presentations
		Expert #4 No, and I regard the evidence base thus far as insufficient
		Expert #5 N/A
		Expert #6 (no response)
		Expert #7 I am not aware of any and looking at the ClinicalTrials.gov website there appear to be 5 ongoing but none in the UK
		Expert #8 (no response)
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1 This would not be needed on every patient with an indwelling urethral or suprapubic catheter, only those who have shown to have increasing problems with recurrent infections or blockages. With my case load of approximately 70 catheters being changed a month. I have 10 patients using the URO-SHIELD with visits to the hospital being spread over a 3 month period for catheter changes
		Expert #2 Gage H, Avery M, Flannery C, Williams P, Fader M. Community prevalence of long-term urinary catheters use in England. Neurourol Urodyn. 2017 Feb 1;36(2):293–6. stated that In England, at least 90,000 community-dwelling people use long-term urinary catheters, most of who are older adults and/or affected by neurological conditions

		4% of community dwellers 15-20% of hospital patients may have indwelling catheter It would be whether we use to prevent CAUTI's for all catheter patients or whether a criteria is developed for individuals more prone to Cauti's or have recurrent Cauti's
		Expert #3 10-20% of patient with long-term catheter
		Expert #4 No additional comment
		Expert #5 Several thousand in the UK
		Expert #6 We have 1000 catheterised patients in Worcestershire and I guess about 10-20% would be suitable
		Expert #7 I really don't know it would not be suitable for everyone with a catheter
		Expert #8 (no response)
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert #1 None that I can think of
		Expert #2 Already identified as above.
		Expert #3 Cost

		Expert #4 No additional comment
		Expert #5 None of concern
		Expert #6 Needs to be worn for 24 hours but is discreet
		Expert #7 As above
		Expert #8 When looking at patients we felt that they would need to be able to self manage or have a family member living with them who would be able to manage the device with capacity. The device needs monitoring, charging, ensuring it is positioned correctly etc. Carers coming in periodically would not manage this.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert #1 Cost as always is a problem with potential future savings being difficult to prove, against the initial costs
		Expert #2 As discussed above
		Expert #3 No
		Expert #4 No

		Expert #5 Cost
		Expert #6 Responsibility for set up and maintenance costs
		Expert #7 No
		Expert #8 Our team felt that standard care would need to be assessed as being well managed prior to introducing the device and this was not always the case. Funding needs to be in place. Patients need to be able to manage the device and understand how to use it correctly.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert #1 As stated in section 1 an indepth study of bacterial infestation prior to and post use of the device will certainly add to the evidence base
		Expert #2 Yes as outlined previously
		Expert #3 Compare this device with using different catheter in the market that is used for such patients with CAUTI, silver coated catheter, antibiotic impregnated catheter.
		Expert #4 Credible medium-term (one year) independent data with a proper design to evaluate CAUTI and blockage rates
		Expert #5 Larger trials required

		Expert #6 Not that I can think of
		Expert #7 Safety of continuous acoustic waves in the urethra needs to be addressed
		Expert #8 The use with patients with MS.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 – not asked
		Expert #5 Beneficial outcome measures: Reduction of CAUTI Adverse outcome measures: Inappropriate use of equipment Inability of users to cope with the technology Over confidence in the technology leading to decrease in monitoring for infection
		Expert #6 Beneficial outcome measures: Improved quality of life including catheter discomfort and pain and sleep quality and duration Reduction in urine infections and catheter blockages and use of antibiotics

		Reduction in unplanned community visits/attendance at GP, A&E, ambulance service visits We asked these questions once weekly over a 12 week audit period We then compared the incidence of UTI's, health professional contacts with the 6 months prior to the 12 week audit. Adverse outcome measures: ? over 12 weeks
		Expert #7 Beneficial outcome measures: Decreased CAUTI and catheter blockage Adverse outcome measures: Longer term assessment of urethral damage related to acoustic waves and whether this has an effect on erectile function either triggering it inappropriately or damaging it
		Expert #8 (no response)
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert #1 There have been initial problems with the battery pack failing to keep its charge, the company has been very quick in replacing the defective packs.
		Expert #2 I have no experience with regards to the device or technology but have vast experience with regards to catheter care, participating in National Guidance, writing relevant catheter articles for national journals However I have experience using other devices that produce currents in the treatment of continence issues

		Expert #3 Not used
		Expert #4 The device may be awkward for users due to its bulk in an inconvenient location, and perhaps compatibility with electronic equipment such as airport or shop security
		Expert #5 N/A
		Expert #6 We have questionnaires we used for the audit and personal letters form patients if required (with consent)
		Expert #7 (no response)
		Expert #8 (no response)
	How useful would NICE guidance on this particular technology be to you or other NHS colleagues? (MIB question)	Expert #1 I feel if NICE supported the use of this product with its guidance it would be particularly helpful in obtaining necessary funding
		Expert #2 I feel it needs further research and clarity of useful and benefits and who it would be ultimately be aimed at prior to NICE recommending guidance
		Expert #3 Very useful
		Expert #4 They would struggle to form a recommendation with the limited evidence base available.

		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked
		Expert #8 – not asked

NICE National Institute for Health and Care Excellence

Patient expert statement

MT476 UroShield for preventing catheter-associated urinary tract infections

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nigel Cameron**
2. Are you (please tick all that	✓ ☐ a patient with the condition?

apply):	☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Ideal Medical Solutions
4. Did your nominating organisation submit a submission?	✓ ☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ ☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	✓ ☐ I have personal experience of the condition ✓ ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with Secondary Progressive Multiple Sclerosis some 45 years ago and started having associated bladder problems some 35 years ago, eventually culminating in receiving a suprapubic catheter in 2002. This form of catheter is a positive way of coping with day to day life but, as with all catheters, comes with the worry of catheter blockages and Urinary Tract Infections which can happen at any time and anywhere. Blockages can be extremely painful especially when bladder wash outs have no effect which then means the catheter has to be replaced which is an uncomfortable process and can also be painful. On one occasion, an hour after having a catheter changed at home due to a blockage, I contracted septicaemia and was rushed into hospital. There is also the embarrassment of bypassing the catheter on occasions when it has become blocked

	which, again, can happen at any time and anywhere. Any instances I have of UTIs or blockages involve my wife, who is my full time carer, and she has to deal with all the consequences - this could be anything from calling for medical help during the night to dealing with the results of bypassing the catheter - and has experienced many broken nights following ambulances to A&E for me to receive a replacement catheter as an ambulance crew are not trained to replace a catheter. Also it is my wife who has to deal with all the devastating effects of a UTI affecting my MS symptoms as I become completely bed bound and incontinent and require 24 hour care until I recover.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Current treatments on the NHS, to my knowledge, are antibiotics for a UTI and/or a bladder washout for a blocked catheter. In my case a bladder washout has hardly ever worked, no matter how much force is used to try and flush the liquid through it just doesn't move and so the catheter has to be replaced. Care available is usually from the District Nurse during the day but on some occasions when taken into A&E with a blocked catheter at night it isn't dealt with as a priority and waiting time becomes unbearably painful.

10. Is there an unmet need for patients with this condition?	Absolutely. In my opinion as this new technology is non-invasive, not a drug, is easy to manage, and can free up hours of District Nurse visits, ambulance call outs, A&E admissions and potentially a hospital bed, it is exactly the new technology that would help so many people who suffer UTIs and blockages. My GP, who has treated me for years, has described the effect of using this new technology as "transformational" as after so many years of frequent UTI's and hospital admissions I have only suffered 1 UTI since starting the trial of UroShield in October 2018 until the present day.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	This new technology is life changing – for myself and my wife who cares for me - a huge improvement to one's well-being, a confidence booster and not yet another drug to be taken as it is worn outside the body, is painless, very discreet to wear, reduces the need for unexpected catheter replacements and is so easy to use. The Actuator is in place on the catheter at all times and is constantly charged via a fine cable from the Driver; the Driver is charged overnight as I sleep so is fully charged and ready for the morning. Once the Driver runs down later in the day it can be connected to the mains power for recharging, but if I am out and about and away from home I always carry a small, portable, power pack with me (small enough to pop in my pocket) that can be easily connected to the Driver and allows me complete freedom to continue whatever I am doing.

	To reduce the frequent need for antibiotics is also a huge benefit when it is known that too many courses can reduce the effectiveness of the drug which Doctors prefer to prescribe less often now because of this. As soon as I started using this new technology in 2018 I was able to immediately stop taking constant prophylactic antibiotics which was a huge relief. Many District Nurses, on seeing this new technology, have commented that they visit some of their patients almost daily to perform bladder washouts and how this new technology would transform theirs, and their patient's lives, and free up District Nurses to deal with other patients.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Referring back to question 11, perhaps the only slight disadvantage currently is the battery power time if you are away from a power source but as I have described it is very easy to compensate for this by having a small – about the size of a mobile phone - and inexpensive power pack with you.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and	I would suggest any sufferer of regular UTIs or catheter blockages would benefit hugely from this new technology. Both able bodied and disabled people can be affected by bladder issues and this new technology is so easy to use, either by the person requiring it or by their carer on their behalf, and can hugely improve quality of life.

explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not that I am aware of.
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- This new technology is so effective and extremely simple to use
- Care/visits from District Nurses and other medical services including hospital admissions hugely reduced
- It is not a drug
- Ends the need for taking prophylactic antibiotics on a daily basis
- Using this new technology has transformed my life

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies – Uroshield

NICE Medical Technologies Advisory Committee

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	Bladder Health UK
Contact person's name	[redacted]
Role or job title	[redacted]
Email	[redacted]
Telephone	[redacted]
Organisation type	Patient/carer organisation (e.g. a registered charity) ☐x Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☐x Education ☐x Campaigning ☐x Service provider ☐ Research ☐x Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? We have approximately 2,000 members, 1,700 of whom are patients/sufferers and approximately 9,000 followers on social media. Our sufferers are predominantly women but approximately 10% are male. We have members throughout the UK.	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies – Uroshield

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

Patient experiences are gathered by the team during our conversations with them on our Advice Line. We regularly discuss treatment options with our members. The Advice Line is open five days a week between 9.30am and 2.00pm.

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Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

In-dwelling catheters introduce bacteria to the bladder and promote colonization. We regularly hear from members who have in-dwelling catheters and are subject to regular hospital stays as a result of the infections and even urinary sepsis they suffer as a consequence of the catheter.

Constant use of antibiotics in an attempt to keep the bladder clear of infection often leads to antibiotic resistant bugs invading the bladder and frequent courses of IV antibiotics. Frequent urinary tract infection is extremely painful and debilitating. It is disruptive to a life in many ways with sufferers often being unable to work and family lives and relationships suffering.

2. How do symptoms and/or the condition or disease affect carers and family?

Frequent urinary tract infection is extremely disruptive to normal living. It affects personal relationships, work, travel and leisure for sufferers and their families. The risk of sepsis and even death is higher for this category of patients than the general public.

3. Are there groups of people that have particular issues in managing their condition?

Sufferers of Fowler's Syndrome and neurogenic bladder usually have permanent retention which rarely improves over time. As a means of management they are often offered a supra-pubic catheter.

Experiences with currently available technologies

4. How well do currently available technologies work?

Antibiotics are the mainstay for prevention and treatment of urinary tract infection. They are currently the only option available to GPs when managing those with in-dwelling catheters. Those with in-dwelling catheters have frequently recurring UTIs and therefore often have to take repeated courses of antibiotics or have to be admitted to hospital if these fail to be treated with IV antibiotics. With the rise in antibiotic resistant organisms and the frequency of use of antibiotics among this category of patients, regular hospitalisation is inevitable.

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5. Are there groups of people that have particular issues using the currently available technologies?

Those with recurrent catheter-related urinary tract infection frequently have antibiotic-resistant infection. They then have to be admitted to hospital for treatment via an IV which is not only costly to the NHS, it is also extremely disruptive to day to day living.

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

For those who have trialled this device, it seemed to lessen the occurrence of infection and the need for antibiotics. In our opinion if Uroshield was an option much earlier in treatment, some of the infections suffered by this cohort of patients would be much reduced.

7. For those <u>without</u> experience of the technology being assessed, what are the expectations of using it?

That their risk of infection is greatly reduced. As a result, they and their families will experience better quality of life. The mental health issues experienced as a result of continual pain and infection are reduced.

8. Which groups of people might benefit most from this technology?

Those who live with in-dwelling urinary catheters as a result of urological disease ie. those who suffer from neurogenic bladder or Fowler's syndrome. Those who require an in-dwelling urinary catheter for a period of time following an operation.

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Hospital admissions are costly to the NHS. They also limit a sufferers ability to work and have a stable and fulfilling family life.

Key messages

10. In up to five statements, please list the most important points of your submission.

- **Catheter-related infection is thoroughly debilitating and at times life-threatening.**

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- **Uroshield can be a valuable tool in prevention of catheter acquired urinary tract infection.**
- **Uroshield can be a valuable tool in reducing the use of antibiotics among this category of patients.**
- **Regular hospital admissions for IV antibiotics limit the sufferers ability to work and have a stable and fulfilling family life.**
- **Choices to limit infection for this category of patients are very limited at the moment. Patients, when given the option, would like to have a solution other than frequent antibiotics.**

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including Diagnostics Assessment) and will be held on the Institute's databases for future reference in line with our privacy notice.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT476 UroShield

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*

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1.	10/06/2021	Meeting with the company to discuss the clinical submission	The EAC sent a list of questions in advance of the meeting.	Written responses were provided by the company and are reported in Appendix 1
2.	14/06/2021	Clinical expert engagement meeting	The EAC sent a list of questions in advance of the meeting. These were discussed in detail during the meeting.	Notes from the meeting are reported in Appendix 2
3.	15/07/2021	Company Engagement meeting	A list of questions was sent to the company in advance of the meeting. Some written responses were provided in advance of the meeting and the remainder were discussed during the meeting.	Notes from the meeting are reported in Appendix 3
4.	15/07/2021	E-mail to the company (sent via NICE)	In the economic submission on p17, "Community Onset CAUTI" section, there appears to be some missing text between the lines: "bacteraemia require hospitalisation). CG139 also assumed that the cost of replacing a CAUTI would be..?.... required the costs were all uprated to 2019/20 prices using the HSHC and NHSCII inflation indices" Can you please double check what the missing bit says?	Corrected Response provided by the company Community onset CAUTI The costs of community onset CAUTI were derived directly from CG139 who in an economic model of intermittent catheterisation included a detailed costing of treating community developed CAUTI. Whilst the resource use was based upon CAUTI developed in intermittent catheterisation, NanoVibronix considered there is no reason to assume that the costs of CAUTI would be the different for treating CAUTI in long-term indwelling catheterisation. The costs included in CG139 included initial treatment, first line antibiotic resistance, multidrug resistance and bacteraemia (both multidrug resistance and bacteraemia require hospitalisation). Costs were all uprated to 2019/20 prices using the HSHC and NHSCII inflation indices. Real world evidence from Da Silva presented in Part 1 included qualitative feedback that patients with recurrent CAUTI in the community tend to be more likely to require significant clinical care, including hospitalisation, when being treated for CAUTI, compared to patients who rarely have CAUTI. This finding, in combination with the rate used for recurrent CAUTI in the model being as

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				low as it can be, means the costs of CAUTI for patients with recurrent CAUTI will be conservative. A large and unique data set was collected in England between 2009 and 2012 for a study on catheter related quality of life.
5.	15/07/2021	Follow-up e-mail from EAC	A number of questions relating to the economic submission were follow-up up via e-mail.	Details of responses are noted below (Appendix 4)
6.	20/07/2021	E-mail to the company	Query around technical details of the device and CE marking 1. The Uroshield device is CE marked (expires in 2024), are there currently any plans to apply for a UK Conformity Assessment (UKCA) which will be required post 2023? 2. The company submission states that the changes/updates to the device do not have any impact on device mechanism of action or clinical outcomes. Can I just clarify briefly what improvements were made to the driver functionality in 2018 (did it improve battery life or something similar?) Could you also give a brief explanation of what the change 'Implementation of EMC IEC 60601-1-2 rev. 4.0 standard' and what the firmware updates	The company provided responses to these questions, the detail of which has been incorporated in the Assessment Report where appropriate (see section 2: Overview of the technology and Section 3: Clinical Context)

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			entailed? I just want to make sure that, although the changes may not have impacted the mechanisms of action in terms of the ultrasound action, that none of the changes had an impact on device performance.	
3.	21/07/2021	E-mail to study lead (Dr Shenfeld)	Query sent to study lead around the methodology and infection measures. • Can you provide some detail as to why the trial was stopped early? • Do you have any information on why some of the clinical data collection (specifically the urine cultures) were not done for the patients in the study at all time points? • In terms of the infections, are all infections at different time points new infections? Or are some of the infections persisting in patients from a previous time point?	Response received to say it would take time to look for the answers to these queries. The EAC will further update the correspondence log with any information received.
4.	22/07/2021	E-mail to the company	Do you have details of the research project currently active in Southampton Do you have the numbers of NHS trust (number of devices) where UroShield is being used	Company has provided additional details which have been incorporated into the assessment report where appropriate (see section 8.2: Ongoing Clinical Trials)

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5.	22/07/2021	E-mail to study author (da Silva 2021)	Details of the unpublished study have been shared with NICE and the EAC and the study author has provided some additional study details which have been reported in the Assessment Report where relevant. As this study is unpublished, the EAC has sent an e-mail to check the confidentiality status of the data.	The study author has confirmed that nothing that has been provided to the EAC/NICE needs to be treated as confidential.
6.	23/07/2021	E-mail to company	Query to confirm whether Markowtiz study and Rosenblum study are indeed the same study.	We can confirm that the Rosenblum abstract is the same study as Markowitz, as they were required to provide an interim statement on study progress and any information reported would have been subject to change before the final data collection, study report and publication. In the Part 1 Clinical submission, this earlier interim information from Rosenblum was excluded - and the completed published RCT with Markowitz lead author was included.
7.	28/09/2021	E-mail sent to study investigator	An e-mail sent to the study investigator for the ongoing study NCT03785262 to enquire as to the study status	The investigator reported that the study stopped due to Covid and there are currently no evaluable results.
8.	28/09/2021	E-mail sent to study investigator	An e-mail sent to the study investigator for the ongoing NIHR study to enquire as to the study status	No response received

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9.	07/10/2021	E-mail sent to the company	Following the lead team meeting, the EAC sent an e-mail to the company to seek clarification on a couple of issues: 1. There was a query over the reason for changing the actuator every 30 days. Is this something there is evidence for at all? 2. Similarly, can we just confirm that if a patients catheter is changed before 30 days, the same actuator can be replaced on the new catheter? This is what we have in our meeting notes from the company however the Instructions for Use state that the actuator should be changed whenever a catheter is changed. Could you just provide some clarification and context on this please? 3. One of the team raised the issue of an ongoing study in Coventry and whether there was any more detail on this. Could we just clarify that the only study in Coventry is the one reported by DaSilva which has now been completed? Are you aware of any ongoing work there at all?	1. When the actuator was being designed, the clinicians involved practiced in the US market so they provided feedback that long term catheters were required to be replaced every 30 days. This was supported at the time by the US Agency for Healthcare Research and Quality (AHRQ) who produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used. As the US is the largest global market, NanoVibronix accepted the advice of the clinicians, which resulted in the piezo-electric material selected by the designers and engineers producing ultrasound waves consistently for a minimum of 30 days. This in turn, led to the recommendation that the actuator should be changed every 30 days when the catheter was changed. However, the AHRQ has more recently issued further guidance based on literature reviews which challenges the 30 day change. Please see: Appendix F. CAUTI Prevention in Long-Term Care: Frequently Asked Questions | Agency for Healthcare Research and Quality (ahrq.gov) Statements in this document: ***Time between replacements*** *The recommended time between catheter replacement depends on local policies and varies significantly between centres (Palka 2014; Willson 2009). This discrepancy in clinical practice reflects a lack of evidence to support the early or late replacement of long-term urinary catheters in the reduction of adverse outcomes. The Infectious Diseases Society of America (IDSA) states there is currently insufficient data to recommend a specific time interval between long-term catheter or suprapubic catheter replacement*

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				(Hooton 2010). A shorter time interval between catheter replacements may reduce the development of a biofilm that can act to harbour bacteria, and may also reduce the likelihood of mechanical blockage. However, the tissue disruption caused by more frequent catheter replacement could contribute to the development of CAUTI and other adverse outcomes. ***Should we change urinary catheters every 30 days?*** *There is little evidence to suggest any benefit that routine catheter or drainage bag changes prevent CAUTI.*[10] Please also see https://www.ncbi.nlm.nih.gov/books/NBK545495/ Because the majority of health systems outside of the US recommend changing the catheter based on clinical indications, such as infection, obstruction, or when the closed system is compromised, NanoVibronix have continued to develop the piezoelectric component of the device to meet the requirements of the wider global market so that it continues to operate consistently beyond the 30 day period and up to a maximum of 90 days. 2. The Instructions for Use do state that the actuator is for use with a single catheter only and should be disposed of when the catheter is replaced. However, data from NHS clinicians and patients in real world use has revealed that the patients, their carers and clinicians have been changing the catheter at different intervals and replacing the existing actuator on the new catheter. What had previously not been realised was that many patients have frequent catheter changes due to blockages, with some patients blocking frequently over a short period of time. This would mean that actuators would need to be changed even through they were functioning perfectly, leading to unnecessary cost.

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				As the actuator continues to function properly from the old catheter to the new, it does make economic sense to use the actuator for as long as possible and as you have stated, this information was provided to the NICE team. Further positive data from patients who are using UroShield in a real world setting is that they experienced reduced blockages or obstructions in the first few weeks of using UroShield and then very few or no blockages with continuous use. This would support the data from existing studies and information we are receiving from our most recent NHS study of patients using UroShield for the first time. Obstruction is usually caused by encrustation due to bacterial contamination so as the ultrasound is targetted at preventing the bacteria from adhering to the catheter surface, the bacteria are unable to colonise in the lumen of the catheter and do not obstruct the passage of urine. This additional benefit of UroShield helping to prevent catheter blockages which are a considerable clinical, social and economic issue sits appropriately alongside the primary indication of preventing CAUTI. This improved understanding of how UroShield works for patients in the NHS setting will inform the next iteration of the Instructions for Use for the UK users of UroShield. 3. You are correct that the study reported by Associate Professor Da Silva was the study that has now been completed and this study was published a few months ago. Although the DaSilva study was completed at Coventry University, the study gathered data from NHS patients in different community care settings who had been using UroShield for many months. https://www.researchgate.net/publication/353646883_Medical_Surgical_Urology_The_Effectiveness_of_UroShield_in_Reducing_Urin

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				ary_Tract_Infections_and_Patients%27_Pain_Complaints_Retrospective_Data_Analysis_from_Clinical_Practice There is no further work being undertaken there at the moment.
10.	11/10/2021	Email sent to the clinical experts	Following the lead team meeting, an e-mail was sent to clinical experts to request information around the number of blockages experienced by patients: 1. In your experience, what proportion of patients with a long-term indwelling catheter would experience a blockage that requires a catheter change/staff time? 2. Appreciating that some patients will have a greater number of blockages, could you provide an estimate of the number of blockages a patient might experience in a month? 3. Could you provide some information on the number of blockages that would require a catheter change and how many can be managed by other means (catheter washouts)? 4. Could you provide an estimate of the number of blockages that occur in addition to CAUTIs requiring treatment?	Answers from the experts are collated and reported in Appendix 5.

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Appendix 1. Company Start-up Meeting Notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Medical Technologies Evaluation Programme

Company Start-up Meeting
MT476 for Preventing Catheter-Associated Urinary Tract Infections (CAUTI)

This document summarises the discussions that took place at the company post clinical submission meeting for MT476 UroShield, which took place on Thursday 10th June 2021, 16:00-17:000pm. Written responses were supplied by the company in advance of the meeting.

Attendees:
NICE

- Bernice Dillon,
- Ying Ying Wang
- Dionne Bowie

Cedar (EAC)

- Rhys Morris,
- Ruth Louise Poole
- Susan O'Connell

Company

- Trevor Stanley
- Alexandra Ibbotson
- James Mahon
- Sarah Bolton

Discussions centred around 4 key themes

- Evidence
- Implementation
- Contraindications for use
- Device specific queries
- UK pathways

Evidence

1. Do you know when the Da Silva paper is likely to be published? Will we be able to access additional details, such as the study design/protocol and baseline patient characteristics?

Company written response prior to the meeting

- The study has been accepted for publication and will be published in the next few months and the Protocol is attached
- Baseline characteristics include;
    - Does the patient have a current CAUTI
    - Number of urinary Tract Infections

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- Number of catheter blockages
- Number of catheter changes
- Number of bladder washouts
- Number of separate antibiotic prescriptions
- Number of days taking antibiotics
- Number of hospital visits
- Number of nights spent in hospital
- Have any hospital visits required the use of an ambulance
- Number of district nurse callouts
- Number of GPs or out of hours doctor callouts
- Type of Catheter
- Sex
- Age
- Medical Condition
- Other Details

There was a follow-up query from the EAC on the baseline characteristics as these are not reported in the draft paper. The company have discussed this with the author who will provide this data and have provided the contact details for the principle author.

1. Do you know when the Wilks (ongoing) study is likely to finish?

The Wilks study was due to commence in 2020, however, it needed to be delayed due to the pandemic. Recruitment commenced in May 2021 and each patient will use Uroshield for a minimum of 90 days resulting in a total study time of 16 weeks. This would place the study finishing date in September 2021.

2. Does any of the evidence show comparative effectiveness (against a control group) when UroShield is in place for longer than 30 days?

No.

The issue that we confront when discussing the study protocols with clinicians is that they are selecting patients who suffer from recurrent CAUTI and they do not believe it is beneficial or ethical to use a sham device on these patients.

The clinicians prefer to compare the present standard of care with antibiotics as their baseline for treatment of the recurrent infection before using UroShield as the active device. Data is collected on the outcomes before, during and after using UroShield and the significant reductions in infection, blockage and pain result in the patients continuing to use the device.

The patients' own baseline standard treatment for CAUTI therefore becomes the control and the baseline data is compared with the data following the active treatment with UroShield.

Practicalities of implementation and use

3. What does training involve - for clinicians and for patients? How much time is required?

Clinicians are trained by one of our clinical team, device operation is simple and requires minimal training but offers a forum to answer any questions.

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Patients are trained by clinicians on the basic operations of the device.

Training on UroShield takes up to 30 minutes for clinicians and up to 10 minutes for patients.

We are also developing a short video to support clinical training remotely at staff convenience.

All training content is included in the IFU.

4. Has patient compliance been assessed? What were the findings?

Results from the Da Silva study and from patient testimonials described good patient compliance, however, this has not been measured in a previous study but will be included in the Wilks study.

The benefits for the patient of having no infections and a reduction in blockage pain and discomfort is a great incentive for the patient or carer to achieve compliance. However, there will be patients who are poorly and will be dependent on a clinician or carer. Where a carer is responsible for the patient, additional effort is made to train the carer.

5. You note that “in many cases” patients and carers can manage the device themselves following training. What reasons might there be for people not being able to manage the device?

Patients who have underlying health problems which impair their mobility and patients who are poorly or have acute illnesses, may find operation of the device difficult and require support from a carer.

6. How do ambulatory patients use it if they don’t have a pocket for the driver? Could either of the cables (charging cable, actuator connection cable) present risks associated with snagging or tangling?

Ambulant patients have their own preferences with regard to where they put the driver so it is out of sight. A lanyard is provided with each device however patients find a solution that works for them.

There have been no reported issues with cables snagging or tangling, we believe this is because patients are already familiar with management of their catheter and catheter bag.

7. How can patients ensure device remains charged and functioning for periods longer than 6 hours (e.g. overnight)?

Patients connect the device to the mains whilst they are sleeping which removes the need for recharging.

8. Could the device present a problem when the patient goes through airport security?

A longer term UroShield user has reported that they have travelled to other countries whilst wearing the UroShield device. At the airport security zone, they make the staff aware that they have a medical device and the staff scan the driver using a hand scanner as this is the only part of the device that they are concerned about.

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They have never had a problem going through airport security.

9. Could the actuator become dislodged (eg with vigorous movement)? Are you aware of this having happened in any patients?

There have been no reports of the actuator becoming dislodged due to vigorous movement. On the inside of the actuator, there is an adhesive strip which secures the actuator to the catheter and prevents it from moving or becoming dislodged.

Contraindications/risks

10. What is the minimum age (if any) for use of UroShield?

Whilst the UroShield device is not contraindicated for paediatric use, at present, the device is focussed on patients who are a minimum of 18 years old.

11. Your submission states “UroShield should not be used for treating an active urinary infection (page 9), and the IFU states “UroShield is not intended as a treatment for an active urinary tract infection”. The pathway described on pages 13 and 14 (Fig. 3.4 and 3.5) refers to “Urinary tract infections in people aged 16 years and over – with a urinary tract infection – with a catheter” and confirmed as CAUTI. Please clarify whether the device can be used when a patient has been diagnosed as having a CAUTI, and whether additional criteria or cautions apply in these circumstances.

In order for UroShield to be most effective it should be used when the infection has cleared and when a new catheter is inserted.

To clarify this, we have amended FIG 3.5 Supporting Pathway from the Part 1 submission below. Patients who meet the criteria for recurrent infections would be prescribed UroShield, standard care would then be used to clear the infection before commencing preventative treatment with UroShield.

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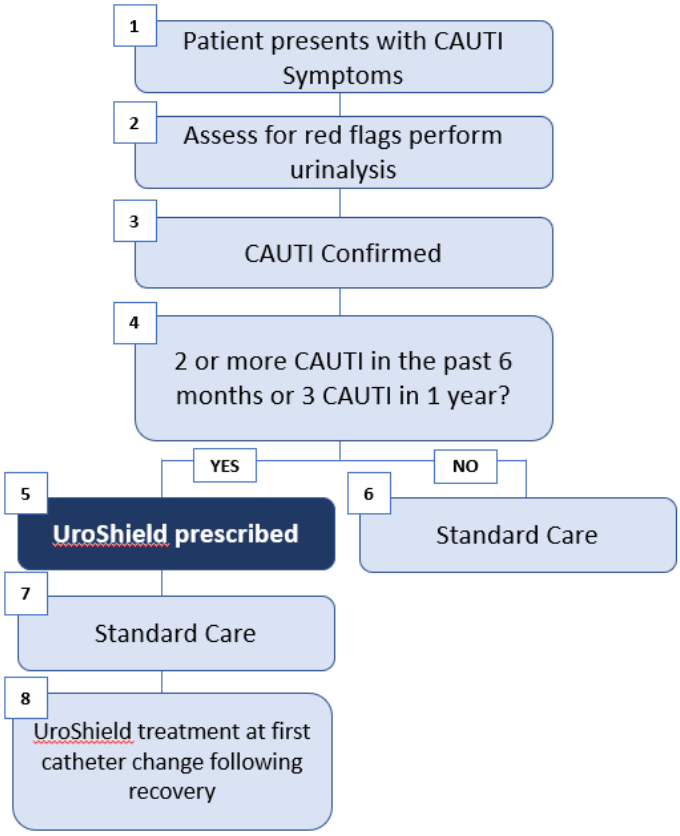
At the first catheter change following recovery from the infection, UroShield treatment would start



12. According to the IFU, the driver “is not intended for use in the presence of flammable liquids” (Section 6.1 Product care), and users are instructed “Do not use UroShield in the presence of flammable materials and liquids” (Section 3.2 Safety/warnings). Could UroShield present a risk to people who use paraffin-based emollients?

The UroShield does not present any risk to people using paraffin-based emollients. This safety/warning was added as a regulatory requirement because the driver includes an electronic board. This precautionary warning is for extremely rare cases that an electronic part (e.g. a capacitor) may burn and create a momentary spark that may start a flame in the presence of flammable surrounding gas.

13. Is there any risk to nearby tissues of operating an ultrasonic device nearby? Could long-term continuous stimulation:

The UroShield device operates with low intensity/low frequency ultrasound which has an impeccable safety record. Ultrasound intensity in UroShield is lower than the level that may cause any change/damage to nearby tissue.

a. affect reproductive organs/fertility?

   No

b. be used in pregnancy?

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Yes

c. increase risk of stricture?

No

d. increase risk of malignancy?

No

e. affect (trigger or damage) the erectile mechanism?

No

14. Can UroShield be used on or near a person with a pacemaker or implantable cardiac defibrillator?

Yes, the low frequency ultrasound will not affect these devices.

Driver/battery/actuator characteristics

15. What was the “hardware product upgrade” that led to production of a new version in November 2019? (Page 6 of Company evidence submission). How might any other previous iterations of firmware or functions have impacted on outcomes?

The UroShield 3.0 was introduced with a new case redesign including higher ESD (Electric Discharge) 15KVolt immunity to meet new regulatory requirement of EN/IEC 60601-1-2, 4th Edition.

None of the changes in hardware or firmware had any impact on the UroShield treatment protocol.

16. According to the IFU (Section 5 Product features), the battery can be fully charged >500 times, and the lifespan of the driver is dependent on the battery. Could a driver be used by different patients (returned, cleaned and reused)?

Yes, the driver can be cleaned and reused across different patients if required.

17. The IFU (Section 5 Product features) says the battery “can be” fully charged in approximately 2 hours. How long does it take to recharge the battery if the actuator is in use whilst charging?

Fully charging the battery from empty during UroShield use takes approximately 4 hours.

18. The IFU (Section 5 Product features) indicates that the device can be powered by the internal battery for up to 6 hours, but that “operational time may decrease over time when running on the battery” – has this degradation been modelled?

This expected degradation in battery performance is based on Lithium-ion batteries which are used in the UroShield device and similar to batteries which are used in the majority of smaller electronic devices in everyday use. The battery providers model the capacity degradation rates and provide us with the graphical data.

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This is part of the technical specification for the battery - ≥500 cycles (0.5C5A) & ≥800 cycles (0.2C5A)

19. Can supplementary battery charging cables be purchased separately (eg in case of loss)?

Yes. A supplementary manufacturer approved power supply can be purchased separately.

20. Could you clarify whether the patient is likely to be able to feel the vibrations? The patient FAQ section of your website indicates that “vibrations are so low-frequency, nothing will be felt so long as the clip is placed 4-6cm from entry point”. However, the IFU (Section 7 Operation) and Quick Start Guide advise that the distance between the point where the catheter exits the body should be 2-3 cm in women, and 5-10 cm in men.

The patient does not feel any vibrations from the UroShield ultrasound applied to the catheter regardless of the distance of placement in relation to catheter entry point. The distances are to ensure that the actuator does not come into contact with the entry point of the patients body.

The statement on the website will be corrected to agree with the IFU.

21. Are there any differences in placement and/or operation of the device depending on where the catheter is inserted (urethral or suprapubic)?

There is no difference in actuator clip placement on the catheter whether using a suprapubic or urethral catheter.

22. Is there dampening of the ultrasonic waves as they move away from the actuator (have you tested whether the length of the catheter might impact on effectiveness)?

Ultrasonic waves attenuate as they propagate through any medium. Empirical testing of the UroShield has demonstrated that ultrasonic waves travel throughout the entire catheter length inside the bladder and in the opposite direction from the actuator, along the tube to the collection bag.

23. Do any parts of the system generate heat, for example whilst connected to an A/C power source? Is surge-protection built in?

No noticeable heat is generated during operation or connection to the A/C. Surge Protection is built into the charger.
Surge: IEC61000-4-5,EN55024:2010,IEC60601-1-2:2014 ±2KV line to line. No damage or performance degradation to adapter.

24. Please confirm whether “single-use” (of the actuator) refers to per patient, or per catheter?

Single use relates to the patient.

Actuator changed every 30 days

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Some indications that the actuator can extend the life of the catheter. The catheter will be changed as often as necessary (determined by patient need). Actuator does not need to be changed at every catheter change.

- Risk for when patient's catheter only at 90 days?

Charging the device?

- Initially though all patients with catheters were not mobile but now patients can be more mobile and don't seem to have a problem with using the device.
- Not ideal for patients to not charge the device within 6 hours but effects of ultrasound continue to have an impact if device stopped for a short while.

Fine to use the device with antibiotics. Some non-UroShield specific evidence that the effect of ultrasound can also improve the effect of antibiotics.

Standard approach is to clear any infection and then attach a device to the new catheter to prevent future infection.

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General Question on UK pathways

These are notes from some additional questions which arose during the course of the meeting around how the device was likely to be used in the NHS.

The company indicated that they considered it would be

- Predominantly patients who are referred to hospital to see a continence nurse/continence advisor
- Based in the community setting
- Patients living at home/care homes/nursing homes who suffer from recurrent infections and are living with catheters
- Catheter care will be managed by the community nurse/district nurses etc. so will be managed in the community
- Possible sub-populations will be investigated in the economic analysis

The company noted that the economic analysis will be done in both the community and hospital settings but anticipate that the biggest impact will be in the community setting.

The discussion moved to understanding long- and short-term catheter use and how this might have an impact.

The company noted that for short-term vs long term catheter use:

- Anybody who uses a long-term catheter is at increased risk of CAUTI
- Short-term use perhaps prior to surgery to reduce risk of infection before, during and following surgery?

The EAC queried what defines long-term and short-term?

- The company confirmed that long term is anything more than 28 days

What proportion are long-term?

- 100% in the UK at the moment

The EAC queried whether there is a potential overlap with recurrence and long-term catheter use when it comes to defining ‘high-risk’ patients?

- Possibly but patients could have recurrent infections but not be deemed high-risk
- Some definitions of high-risk are provided in the company submission – EAC would like some guidance on how those factors influence risk and to what extent.

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Appendix 2. Clinical Expert Engagement Meeting Notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Expert Engagement Meeting

MT476 for Preventing Catheter-Associated Urinary Tract Infections (CAUTI)

AGENDA

- **Welcome and introductions**
- **Questions for the professional experts by theme: (see below)**
- The condition (catheter associated urinary tract infection)
- Understanding the clinical pathways
- Integrating the technology into the clinical pathway
- Understanding the evidence
- **Next steps**

Attendees:

NICE

- Bernice Dillon,
- Ying Ying Wang
- Dionne Bowie
- Chris Chester
- Tara Cernick

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Cedar (EAC)

- Rhys Morris, Cedar Director
- Ruth Louise Poole, Senior Healthcare Scientist
- Susan O'Connell, Senior Healthcare Scientist

Clinical Experts

- Mr Mustafa Hilmy, Consultant Urological Surgeon, York Teaching Hospital
- Prof Marcus Drake, Professor of Physiological Urology, University of Bristol
- Dr Catriona Anderson, Portfolio GP, Focus Medical Clinic
- Elaine Sutcliffe, Continence Team Leader, Hereford and Worcestershire NHS

Questions for Discussion:

NICE gave an overview of the project and explained the EAC would review the Clinical and Economic evidence adoption of UroShield.

- **The Condition**
- What is the estimated CAUTI prevalence in incidence in the UK?

One expert noted this should be reported in NHS statistics and in the literature. Majority are in primary care. An ambition would be to reduce gram negative infections by 2021. Interested in how UroShield may help.

One expert noted that they may be more common in primary care and community. A second indicated that Urinary tract infection (UTI) is an important cause of morbidity and mortality in the healthcare setting, accounting for 19% of all nosocomial infections. Of these, it is estimated that 43-56% are CAUTI.

The EAC noted they will check statistics available and feedback at next meeting if necessary.

- What proportions of indwelling urinary catheters used in the NHS are Transurethral vs Suprapubic. How do risks of CAUTI's and adverse effects differ between these two types?

One expert noted that for patients with limited mobility in nursing homes and community, suprapubic catheters are in place for many years. Long term catheters might be used for patients who are Diabetic and/or have reduced immunity. Long-term catheters definition PTFE up to 28 days, long term anything from 12 weeks and longer. Some patients have catheters fitted for almost all their life because they are immobile and are prone to infections.

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One expert noted that the majority of longterm catheters are urethral, only around 5% will have suprapubic catheters although there are moves to suprapubic being used in the community. The expert noted this is unusual in a Social Care setting.

One expert noted that suprapubic is the preferable choice for long-term use because of damage to the urethra or strictures from urethral catheters. Suprapubic can only be put in by the Urology department. The experts noted that some procedures can be done under local anaesthetic and some under general and this can impact waiting times.

One expert noted that both transurethral can be used in short/long term catheterisation whereas suprapubic are used for long term management. Patients who are immobile i.e. wheelchair bound are fitted with a suprapubic catheter, which is considered to be easy to care. Long-term catheterization is more commonly seen in residential care setting.

One expert noted that women who have long-term suprapubic catheters are more prone to infections.

Further risk factors discussions: clinical experts noted that comorbidities will need to be considered. The duration of the catheter will be important and will need to consider carefully what the reason for catheterisation is and how it is being done.

- What are the risk factor's associated with CAUTI's
- Do risks differ between sexes and by types of catheters?

One expert noted that the duration of catheterisation and overall comorbidities are influential in the use of long/short term. It is important to consider what the intention of the management is (e.g. post op-orthopaedic surgery). In terms of different risks by sex, sex is a risk factor for different reasons. For example in males, the prostate is a colonisation area which can increase infection risk. In females however, shorter urethral length increases infection risk.

Duration of Catheterisation

- What is the definition of long-term catheterisation?

NICE indicated that the definition of long term catherization is more than 28 days. One expert indicated that short-term catheterisation would be anything up to 28 days.

Two experts noted that there are different types of catheters depending on whether a patient requires long- or short-term catheterisation and this would be factored into treatment planning. Treatment plan would include catheter changes in a community setting every 8-12 weeks.

Referring back to the information previously discussed that patients who are wheelchair bound are more likely to have a suprapubic catheter one expert explained that these patients are prone to infections that are not always related to infection in the catheter. A second expert explained that intermittent catheterisation should also be considered and patients may not have an indwelling catheter in place for long but may have regular episodes requiring intermittent catherization.

Experts agreed that there may be more than one problem regarding the catheter (e.g. blockage). The close drainage system can help with infections, you're not disconnecting and reconnecting the catheter constantly.

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The EAC noted that the literature papers vary in the definition of long-term dwelling catherization. This will be reported and considered appropriately.

- **Understanding care pathways**
- What is standard care for preventing CAUTI for people with long-term catheters in the NHS?

One expert noted that catheterisation will be done in clinic or ward environment or in the community by the district nurse and the patient will receive a passport which outlines management plan. After the insertion, the care for catheter is then moved to GP. Regular checks on the catheter will then be done via the GP/district nurse.

One expert noted that for suprapubic catheters, the procedure is an elective surgical procedure done under local or general anaesthetics. The first catheter change will be in hospital. After that, the district nurse will check it every 3 months. People are referred from primary care to secondary care for the procedure.

NICE noted that they have produced an adoption report shared in chat As part of this, the NICE adoption team interviewed 7 professionals who use UroShield. Overall the feedback from the interviews came out to support UroShield.

One expert noted that it is important to prevent catheter blockages. This could be by ensuring the person is kept hydrated and monitoring urine output.

Regular catheter changes are required and catheter maintenance can include use of solutions such as saline or citric acid. One expert noted that this was for preventing blockages and not for preventing CAUTI.

One expert noted that Farcol Fil is helpful for patients and further discussion among the experts indicated a number of methods which can be employed to help reduce the risk of CAUTIs.

One expert noted that Uroshield is not something that would be considered first line treatment for patients, it would only be considered when all other approaches have not worked. This expert reported that all of their patients are in the self-care (at home) setting.

A second expert indicated that this is most likely to be a community led intervention. There may be a requirement to improve the instructions as they may be written in language that is too medical. Good, clear instructions/FAQ's etc will be needed for patients and carers to ensure they very clearly understand how to look after the device and catheters.

One expert noted that certain community settings such as nursing homes or care homes might find it more beneficial. It may be less work to the carer looking after them in this setting. Home based patients may require more support from district nurses

Experts agreed that the Uroshield device may be more common/beneficial in the primary care setting.

- How would you identify patients at high risk of CAUTI?

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The clinical experts noted that it can be very difficult to pinpoint any specific patient risk factors for CAUTIs. One expert noted that types of catherization/UTI can be significant in the elderly population. This can be due to immobility or dementia and these patients can end up being hospitalised.

A second expert noted that infections can be high in the community. The expert noted however that not all problems with catheters are infection related, more commonly it can be blockage/bypassing/pain/encrustation, due to constipation, hydration and encrustation.

One expert noted that there is a daily risk rate of 5% of patients having a CAUTI and 25% will follow onto a UTI.

This was followed on with a question regarding the impact of CAUTIs on staff time and resource.

- How much additional staff time/NHS resource is required to manage CAUTI's in
    - Community/primary care settings?

One expert noted in secondary care 24hour on call at least a couple of patients would be admitted as they are so unwell that they are septic requiring AB's or ICU admission.

For patients waiting for a suprapubic catheter procedure, the waiting time is long and it was noted by the experts that COVID has not helped this. The experts estimate the current waiting time is approximately 9 months. The experts noted that although this may be a small proportion of the total long-term catheterised patients, these are patients who have the highest burden, this can have major quality of life implications for this patient group. One expert noted specifically, that for the small number of patients who need a suprapubic catheters, there can be great difficulties accessing urologists for having suprapubic catheter and these patients have the biggest burden/great needs and this can have a significant impact on patient quality of life. This also means that there is a burden of care in the primary care setting for looking after and managing condition for these patients while they wait for treatment.

- Community/primary care settings?

One expert noted that there is a high impact on district nurses when changing catheters in the community. This is because of a need to tap into resources and Silo budgeting is not recognised by the services involved regarding staffing costs.

A second expert supported this, noting are quite overstretched. The expert also noted an impact on the GP's.

The experts agreed that overall there is limited recognition/awareness of the impact of CAUTI's on district nurse/GP time.

One expert noted that there can be a high rate of unplanned call outs for catheter changes and often patients leave it until late in the day to call for a change.

The experts agreed that there is an effort to try and prevent CAUTI's and the biggest barriers are likely to be cost.

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One expert noted that the Quality of Life implications of having a UTI is huge. I think patients would be highly motivated. Elderly patients might not suffer as much as younger, ambulatory patients – but there's not much qualitative data to back that up.

The EAC queried whether there was any benefit/situation where uroshield might be used as a first line treatment?

One expert noted that in their practice (with a specialism in women's health) the majority are persistently (chronic) UTIs. The expert noted that they have to raise the possibility of prevention. Experts report that there are approximately 90k catheter users in the UK due to aging population. Once they have a biofilm in uroepithelial cells in their bladder. 269 million (1.7million). This expert raised the question of why uroshield should be considered a last ditch (after recurrent infections) but instead take a more preventative approach. This is particularly important as there are situations where things progress so far they cannot be cured.

- Secondary care?

Compared with an equivalent population with indwelling catheters, who do not experience any CAUTI's?

One expert noted that they only see the patients who are significantly unwell and who may need antibiotics or infection management. They will be in hospital for a few days and there will be treatment planning, discharge planning, discharge care.

EAC asked – what is the rational for treatment options in the pathways?

- What would you need to see to consider this as a first line treatment option?

One expert noted that the definition UTI does not refer to CAUTI. Usually use this as a criteria to refer patient for further investigation by secondary care. So >3 UTI's would get referred. These are the ones who are being sent to secondary care – the ones who require more resources, are a higher burden etc. Not sure why not used in all.

Experts noted that they cannot investigate all infection within the community. Recurring infections in secondary care -mean more work, more resources to be part of their treatment.

One expert noted that call outs for catheter problems may or may not be related to a CAUTI. If patients drink more, were not constipated and the catheter was secured – you can usually resolve most issues without UroShield.

- **Integrating the technology into the clinical pathway**

- In which setting or population would you expect UroShield to be most useful?

One expert noted they would consider it to be beneficial in patients who had systematic UTI infection helped within 4-6 weeks using UroShield. No infections after 12 weeks.

One expert who uses the device replicated what had been done in a previous study. The expert noted that they only did a study of 5 patients of long-term people in community of urethral and suprapubic. All of them found benefit from reduction in pain (dry for first time in 4 years). Quite compelling. The expert noted they wouldn't look at UroShield as first line. Asked people to put forward e.g. problematic catheter change. Several people declined because were told it was a trial.

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NICE noted that most patients may need UroShield. There are some indications from a clinician which suggest that it would be based on number of CAUTI's per year, indwelling catheters for more than 90 days, and antibiotic use.

One expert noted that people with asymptomatic UTIs may present with cognitive blunting and more subtle signs than symptomatic UTIs (fever, frequency, urgency, tendency at renal angle of suprapubic).

- Do you expect UroShield being more widely used in the NHS in the future?

One expert noted that it might be possible to identify some patients who might benefit from using the device earlier in the pathway.

The EAC queried antibiotics use in long-term catheterisation?

One expert noted that antibiotic resistance is a big problem with long-term catheterisation and that they wouldn't want to go down the route of broad spectrum antibiotics. A second expert noted that you would use antibiotics such as Nitrofurantion.

One expert noted that they use D-Mannose and indicated there is evidence that it is as effective as nitrofurantoin but the data are not from good studies. The expert indicated that they do try to get patients on naturopathic medications where possible because they do no harm. A second expert agreed that D-mannose is incredibly useful. Another expert noted they have used it but not routinely.

One expert queried whether there was any comparative data of UroShield vs methanemic methanemic acid – antiseptic action (used in TDS) in catheter.

One Expert reported that apart fromcleaning, changing, there's no alternative to prevent in long-term. Silver coated catheter are changed every 4 weeks. Patients are given prophylactic antibiotics for 3 months – that's not an option for long-term catheter for recurrent infections. The experts agreed that they are seeing more and more antibiotic resistance.

Additional Questions

- Is there any barrier that may prevent the use of the device in the NHS?
- How compliant do you think patients are (or would be) in keeping the device charged and running 24hrs a day?

One expert noted that in a small study they conducted (n=5) patients were totally compliant as they were desperate for improvement.

Other experts agreed that they thought compliance would not be a problem as many patients in this group are desperate for a solution and for improvement in quality of life.

- How do they keep the battery topped up overnight?

- **Understanding the evidence**

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Gauge et al. (2017) report that “unplanned catheter-related events” occur regularly in NHS patients in the community. What proportion (%) of these events would you expect to be attributed to CAUTIs?

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Appendix 3. Company Engagement Meeting Notes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Company Engagement Meeting

MT476 Uroshield for preventing catheter-associated urinary tract infections

Attendees:

NICE

1. Bernice Dillion
2. Ying Ying Wang
3. Dionne Bowie
4. Chris Chester
5. Farhan Jamadar

(Cedar) EAC

1. Rhys Morris, Cedar Director
2. Dr Susan Peirce, Senior Health Scientist
3. Dr Susan O'Connell, Senior Health Scientist
4. Megan Dale, Senior Health Scientist
5. Ann James, Cedar Business Administrator

Company

1. Trevor Stanley
2. Alexandra Ibbotson
3. James Mahon
4. Sarah Bolton

1. Welcome and introductions

2. EAC clinical evidence review

EAC reported that the evidence that has been identified is aligned with that which the company has submitted. No major differences but acknowledge the limitations of the data and how this may impact the certainty of both the meta-analysis result and subsequently the economic results.

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3. Discussion about the issues raised in the clinical evidence review

NICE noted that there have been a lot of emails between the company, EAC and NICE regarding the submission and additional data and information. EAC and NICE to catch up and ensure all information has been shared.

4. Questions on the economic evidence submission

EAC has checked the economic model inputs/calculations against the written submission.

UroShield is cost saving except in the overall community population. Patients in hospitals have more expensive treatment and stay in hospital, whereas in the community treatment is much cheaper (antibiotics and a catheter change).

4.1. Can the company be more explicit about where in CG139 they have taken the

- Probability CAUTI in the community fails first line antibiotics
- Probability CAUTI is multidrug resistant

The EAC has identified where these costs came from but had some queries around minor discrepancies in the values used. The company confirmed they are likely transcription errors and would be happy with the EAC stated values which were more favourable. The EAC noted that the difference was very small and unlikely to make a difference to the costs.

4.2. Can we quickly discuss where the CAUTI rates from Smith are derived, we can find some but not others.

The EAC had worked this out before the meeting started and the company confirmed the calculations.

4.3. Can we double check whether the value from Chant et al should be 2.6 (2.3 to 3.0) for excess ICU bed days

The company accepted this was likely a transcription error and were happy for the EAC stated values to be the ones in the model.

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4.4. Does the company have any insight as to why the data collection has so many gaps in the Shenfeld study? It is not clear from the report whether the reasons for the urine culture data missing is because they weren't taken?

There was a brief discussion around the literature in general which led into some specific conversations around 3 studies in particular. The company noted no findings from company specific studies done 2016/2017. In the USA, the study findings are reporting good outcomes for patients and clinicians.

- The da Silva paper has been accepted for publication and may publish before completion of the assessment.
- Shenfeld – not clear why this hasn't been published or why the data are lacking in the reporting but will follow up and see if they can get any more information. EAC has been provided with the authors contact details by the company.
- Turan study was not immediately known to the company but they have followed it up and provided a translation. The company provided earlier versions of the device to a number of urologists so that they could use them on patients and collect data along with feedback on the operation of the device. This resulted in small studies, some of which were reported through studies, posters or, as in the case of Turan, published locally in their countries.

There was further discussion between the EAC and company around some minor calculation discrepancies and queries in the model.

4.5. The EAC noted that the economic model reported a total cost for treatment for CAUTI in community £382 but in the submission it reads £372.41 and queried whether this is an earlier calculation?

Company responded that this was likely due to small difference in the model calculations but given the small difference in costs were happy for EAC to use which cost they considered appropriate.

4.6. EAC noted that calculation of the catheter cost in community treatment was not described. How was the value of £5.87 determined? Company has l provided the calculation.

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4.7. Reference Costs for CAUTI hospital treatment are calculated using weighted average for 'kidney and urine infections'. But the EAC could not reproduce the figure given in the submission.

The company has provided the calculation.

4.8. In manufacturer's economic submission, page 34 states "Risk of CAUTI is also important in the hospital setting but only in all patients and those with catheterisation <28 days."

This was explained as the 2 populations 'Hospital – all' and 'Hospital >28 days'.

5. Next Steps

NICE asked whether the manufacturers have any questions for NICE/EAC?

NICE outlined the next steps and key dates following submission of the Assessment Report

- Assessment report sent to company for accuracy
- Assessment report to be checked by 26th July
- Final report by 29th July.

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Appendix 4. E-mail Responses from Company to queries relating to economic submission

EAC Query: We are struggling to recreate the cost of an ICU bed day (£1218) from the 2018/19 Reference Costs. I'm assuming this is a weighted average. Please could you ask James how he calculated this value?

Company Response: We took the weighted average for all critical care beds in 2018/19 (see attached). I just checked and in 2019/20 this had increased to £1,349 and if only adult critical care was considered would be £1,619. Including HDUs and ward based CC this is probably resulting in a lower cost than actuality (see for example page 7 of https://www.wales.nhs.uk/documents/Delivery-Plan-for-the-critically-ill.pdf). Sure you are aware (but just to save any confusion if not) activity in the reference cost sheet for critical care represents days in cc rather than an episode or spell.

EAC Query: Thanks for a very rapid reply, James.
That's what I'd done, but already assumed it was adult-only as all the other data seems to be on adults.

BTW, I think we owe you an apology. Looking more closely at CG139 I realise there is a second table of probabilities relating to community-based patients who conduct intermittent self-catheterisation but do not have spinal cord injury (Table 29). These values for treatment failure (8% and 6%) match the values in your base case and make more sense than the values we thought were being used from Table 25 (8.5% and 7%).

However, the model structure in CG139 is different to the UroShield one. In CG139, CAUTI 1st line treatment can transition directly to 1st line failure (8%) OR MDR (6%) OR CABSI (3.6%) (OR cure, of course). Whereas, in the UroShield model, the transitions are from CAUTI treatment TO 1st line failure TO MDR TO CABSI; i.e. patients can only develop MDR after 1st line failure, and CABSI only from an MDR infection. CG139 and Smith both report CABSI as a proportion of total CAUTI, not as a result of treatment failure, so it has to be treated as independent of these proportions.

Therefore, I think the community treatment costs should be calculated as:
(1st line treatment) + (14% 2nd line treatment) + (6% MDR treatment) + (6.2% CABSI treatment)

The 14% is the proportion of the total cohort who get 2nd line treatment (8% who fail first line treatment + 6% who go on to MDR).

[In another recalculation, the 6.2% for CABSI is because the data from Smith doesn't say how much of the hospital-acquired CABSI was in hospital-acquired CAUTI. The 4.8% is the proportion of total inpatient CAUTI (52,085 incl community-acquired CABSI) who get hospital-acquired CABSI (2,524). AS a proportion of hospital-acquired CAUTI it is 6.6% (2,524/38,084), but that's not necessarily correct either. So I took the half-way value.]

I've been going back and forth trying to get this calculation straight in my head. My HE colleague who was also working on this (Megan) is on leave this week and I thought it would be easier to discuss this with you than to try and explain it all to someone new in Cedar. Do you think it's

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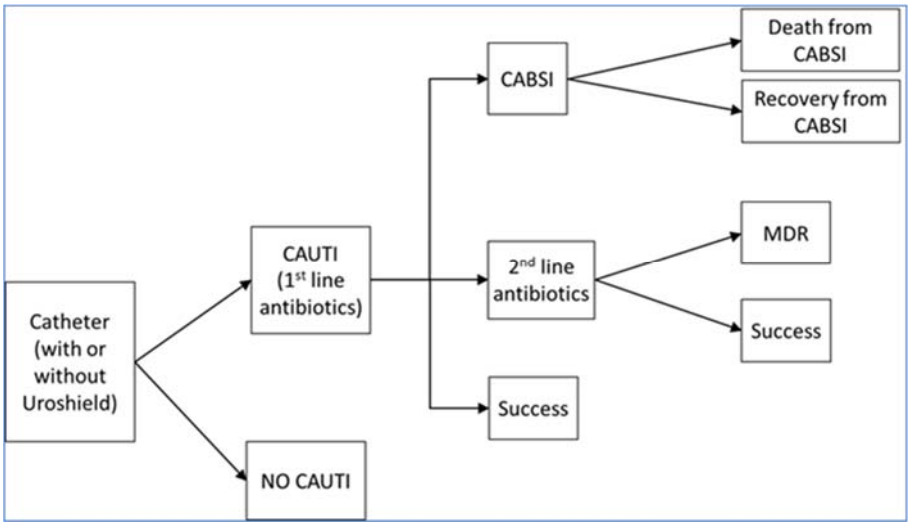
correct that the UroShield model structure should be altered so that CABSI is independent of other treatment failure, and that second line treatment is received by 14% of the cohort?
This obviously increases community treatment costs but not enough to make UroShield cost-saving in this population.

Company Response: It was unclear to me which of the two ways 1st line to 2nd line to MDR to CABSI were modelled in cg139 (ie independently as you have suggested or dependent as I had done). I chose the dependent route as this seemed to make more sense to me (you cannot get MDR unless you fail 2nd line) but mostly because this was the most conservative approach and in all cases where there was some uncertainty I wanted to make sure the argument would end up being that Uroshield was more economically viable than the base case results suggest. With my ERG hat on, if I was reviewing this, I would point out this potential difference in costing approaches, and that the one the company chose was conservative. I would present the alternative results just to show the difference in a scenario but would not put this as a new basecase if it does not change any overall conclusions (unless I strongly felt the company had definitely done it wrong).

EAC Query: I don't have any problem with the progression from 1st to 2nd to MDR.
Working out the percentages correctly was my main question; it should be 14% get 2nd line treatment rather than 8%?

I've redone the model structure as I think it actually is, given the data used for CABSI:



Company Response: I think it depends whether the costs of 2nd line antibiotics are included in the MDR cost. If they are then using 14% would result in double counting. Looking at Table 28 it suggests that costs of 2nd line antibiotics have not been included in the MDR cost in which case we should be using 14% get 2nd line treatment rather than 8%.

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Appendix 5. E-mail Responses from Clinical Experts to Queries Relating to Catheter Blockages

Question	Expert 1	Expert 2	Expert 3	Expert 4
In your experience, what proportion of patients with a long-term indwelling catheter would experience a blockage that requires a catheter change/staff time?	Majority will get blockage	There is research that suggests that 50% of patients will experience regular blockage and I would say that experience reflects roughly this same amount.	This really is an area that is mainly managed by the district nurse teams, so I do not feel I can give you an accurate answer to your questions, from my personal experience. I am afraid my search of the literature hasn't turned up much, there is one mention on PubMed (https://pubmed.ncbi.nlm.nih.gov/7930114/) and although old (1994) nothing much has changed with catheters since then, this publication details 50% of long term catheterised patients experience encrustation and the subsequent blockage, however, this is one of the many areas in medicine which is well recognised yet lacks evidence and statistics. In addition, Wilde et al published in 2016 that 34% result in blockage.	It can go in phases but perhaps 1/3 of catheterised patients will have problems with blockage
Appreciating that some patients will have a greater number of blockages, could you provide an estimate of the number of blockages a patient might experience in a month?	possibly 1-2 per month	In our trusts we run a monthly audit and blockages call-outs range from 1-8 on average.	"Catheter-related urinary tract infection was marginally associated with catheter blockage. Problems reported at least once per person in the 12 months were as follows: catheter-related urinary tract infection 57%, blockage 34%, accidental dislodgment 28%, sediment 87%, leakage (bypassing) 67%, bladder spasms 59%, kinks/twists 42% and catheter pain 49%. Regression analysis demonstrated that bladder spasms were significantly related to catheter-related urinary tract infection and sediment amount, and catheter leakages were marginally significantly and positively related to catheter-related urinary tract infection. Frequencies of higher levels of sediment and catheter leakage were significantly associated with higher levels of blockage, and being female was associated with fewer blockages. Persons who need help with	This may vary form 0-4 times

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			eating (more disabled) were also more likely to have blockages." (https://pubmed.ncbi.nlm.nih.gov/27805758/)	
Could you provide some information on the number of blockages that would require a catheter change and how many can be managed by other means (catheter washouts)?		We attempt to proactively manage the above cohort of 'frequent flyers' with catheter maintenance plans (washout etc) but I would say that a large majority of these calls require a change as our prevention has failed.		When we attend somebody due to catheter blockage, if they are known to have encrustation and maintenance solutions are part of their care plan, then we would try this first. However all other patients we would change the catheter (and examine the tip/for signs of encrustation) and not use a maintenance solution
Could you provide an estimate of the number of blockages that occur in addition to CAUTIs requiring treatment?		Would you like me to tot up the number of call outs to our SPOA over a couple of months for an estimate of catheter complications? The majority of these will be blockages. I could probably get these numbers to you by Weds pm.		Sorry but I am not sure about this

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NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT476 UroShield for preventing catheter-associated urinary tract infections

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from CEDAR External Assessment Centre to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12am, **29th July 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

26 July 2021

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20 c) Urinary tract infections in people aged 16 years and over – with a catheter	C) Urinary tract infections in people aged 16 years and over – with a catheter who suffer from recurrent infections.	We suggest that this description be amended to clarify the difference between a) and b) compared to c)	

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 31 The EAC query why the randomized trial (Shenfeld 2010) was stopped early	Addition of comment The RCT gained approval to recruit 210 patients but due to company commercial strategy, the study was closed at 40 patients.	This description was provided in the submission and as a foot note in the Shenfeld report. The quoted cost for the 210 patient study could not be fully funded by the company at that time and the study was closed at 40 patients. Dr Shenfeld's contact details were provided, along with his willingness to discuss the study with members of the EAC.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 43 Markowitz et al. (2018) The study methodology report however that UroShield was used for the first 30 days and was then followed by standard care for 60 days. So using the data for 90 days would not reflect UroShield use, where the device must remain attached at all times.	Addition of comment. Markowitz et al. (2018) reports infection rates at 30 days and 90 days and the company state they have used the 30-day result to reduce heterogeneity in follow-up times (for comparison, the rates at 90 days were 3/29 with UroShield and 14/26 with SoC). The study methodology report however that UroShield was used for the first 30 days and was then followed by standard care for 60 days. So using the data for 90 days would not reflect UroShield use, where the device must remain attached at all times. In the US, long term catheters are routinely replaced every 30 days which determined the 30-day active use of the UroShield device.	The US health system routinely replaces long term catheters every 30 days. This results in clinicians and patients anticipating improvement due to UroShield within the 30 days between catheter changes. This routine replacement impacted the decision to measure the impact of UroShield in 30 days, followed by SOC for a further 60 days. In the UK and other non-US health systems, long term catheters are routinely changed in up to 90 days and recent UroShield study protocols outside of the US, reflect this difference.	